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ON HEALTH SYSTEMS

III. EXPERIENCES AND CONCLUSIONS

By JOHANNES FRANDSEN

In two previous articles*) I explained firstly the desirability of inducing as many nations as possible to publish reports on the organization, working conditions and working results of their health systems and to circulate these reports as widely as possible; secondly, I tried briefly to formulate such a report on the Danish health system.

It may be natural, perhaps indeed desirable, to conclude an account of this kind with the foregoing as a background by making a contribution — great or small — to the current discussion at meetings and in periodicals on the principles and forms of health organization and work. The character of this discussion is of course affected by wide differences in the illustration and treatment of the question at issue, but it has also revealed considerable mutual agreement in the views of the importance of the questions and in the interest displayed in arriving at the solution that will ensure the most effective health system, which also involves what may be learnt from one's neighbours' defeats and victories.

It is with this in mind, and not for the purpose of holding up our system and our views as the only right ones, that I venture to enter the discussion on the basis of almost thirty years' service as medical chief of the Danish health system, to mention and evaluate some of the aspects of that system to which I attach fundamental importance.

HEALTH SYSTEM IN THE COMMUNITY

As the constitution of the World Health Organization also has it, health is a multilateral concept.

The work to promote and maintain national health calls for the co-operation of wide sections of social life — from economic life to popular education — but particularly for the social organs and institutions that range under the social legislation.

In the practical work of legislation and administration, however, it will be useful, in fact necessary, to confine the scope and function of the health system within fairly narrow bounds.

The treatment, the combating and the prevention of disease and the work to preserve health and full working capacity are the spheres of the health system.

But the collaboration between the health system in the above limitation and social work, which by means of laws and administration aims at relieving poverty, is very intimate — as truly poverty and disease often raise the question of cause and effect.

Every step taken by the community for the purpose of helping the undeservingly distressed individual, no matter whether his need is the result of sickness with subsequent disablement, or unemployment with its consequent defective nutrition, promotes the health status of a community. Social legislation intended to relieve such distress is thus salutary in its effect. Legislation providing the people with the widest possible access to medical treatment and promoting health will simultaneously have a preventive effect against social need. Having embarked upon the course of social legislation it is impossible to overlook the problems of public health.

The dividing line between the two groups of legislation, social and health, is not very distinct, and therefore the terms do not always mean the same in all countries.

From the National Health Service.
Director General: *Johannes Frandsen.*

*) Danish Medical Bulletin, 1955, *2:* 193 & 221.

National sickness insurance is a good example of a social function which in one country is referred to one of these two groups, and in another to the other group.

In Danish legislation there is a natural boundary between health legislation proper and those sections of our social legislation that directly affect public health.

Our social legislation works with a means limit as one of the conditions for its aid.

Our health legislation is aimed at the whole population, makes its offer of health control for expectant mothers and young children regardless of income and wealth, while the hospitals and disease treatment on the whole make it possible in principle for all to receive the proper treatment for their ailments.

The scope and assistance under the control legislation are subject to political considerations.

Of course, a health legislation within the limitations already described may also become a subject of political debate; but considered soberly it would be more difficult to raise this legislation as a banner for either liberal or socialistic ideas and mode of thought. At any rate, a small country like Denmark would not find a satisfactory solution to her health problems along other lines than that of concurrent effort.

One inevitable consequence of our entire disease treatment system is the position of our physicians, with incomes mostly deriving from the national sickness insurance and from the hospitals. Neither in its origin, with the medical profession voluntarily helping to establish our sickness insurance, nor in its subsequent development, has this had any relation to political ideologies. One policy alone has been pursued through the fifty odd years during which this system has been evolved under changing governments and changing political majorities in Parliament: to build up a system for patient treatment that would provide everybody with unhindered access to the best possible treatment, and to establish the most effective prevention of disease. This policy has the additional advantage of being the most favourable one, economically.

The health system as a social organ with its own sphere of activities must find its place within more narrow limits than could be presupposed by WHO's definition of the concept, laid down in WHO's constitution.

On the other hand, it is necessary that the experts of the health system should be able to voice their views to other social organs and institutions when necessary for procuring harmonious and fruitful co-operation.

DISEASE TREATMENT, THE HOSPITALS AND PRACTITIONERS

One sometimes comes across articles, or listens to discussions, from which one gains the impression that by "public health" is particularly meant that section of the health system which comprises prevention in its various forms, health control, housing hygiene, food control, and so on, but deals with the problems of disease treatment as a special subject not calling for the same measure of interest and responsibility in the community.

The evaluation of this question and the choice of roads to follow in order to grapple with it must give differing results according to the individual conditions within each country, including the stage of development at which the hospital system has arrived and the number of medical men.

In the Danish health system the treatment of disease has always been, without discussion or the slightest doubt, one of its fundamental elements, co-ordinate with the prevention of disease and the work of preserving health.

As has been explained in one of the previous articles, legislation has been provided in Denmark to ensure that all have access to proper treatment and nursing.

The hospital system has its net of hospitals spread over the whole country, while ambulant treatment is given by G. P.'s in their surgeries or at the homes of the patients.

The hospitals admit patients only when referred there by their doctors, and on discharge a patient returns to his doctor who is informed by the hospital as to diagnosis and treatment.

Future development will aim at intensifying the co-operation between these two parties by "carrying the hospital work out beyond its walls", at placing the hospital installations in X-ray institutes and laboratories at disposal for extra-mural treatment as an aid to the general practitioners. It is hoped by this means to avoid superfluous hospital admissions, but in particular the aim is, by encouraging this co-operation, to keep the family doctor in constant touch with developments inside the hospitals — and conversely, the hospital doctors derive much benefit from their contact with the G. P.'s and from being made acquainted with the latters' special experience, which otherwise often escapes the hospitals.

Just as the close co-operation between hospital doctors and G. P.'s recognizes and establishes the latter's traditional position as the family doctor, the G. P. has his place as the central figure in the whole of the preventive work, which was initiated by the legislation of the last two decades, concerning health control and preventive vaccination. This principle of the G. P. as a fundamental and bearing factor in the health system, maintained in present-day developments of that system with all its new sphere of activity which prevention has brought about, has been adopted as a logical consequence and a natural evolution of the centuries-old standing of the doctor in society. It would be unreasonable and uneconо-

mic not to attach this large staff of well-trained practitioners to these new spheres. And, what is of greater importance, we succeed in securing the entire medical profession as active and interested helpers in the various domains of disease prevention. We should scarcely have succeeded in getting about 100 per cent adherence to the voluntary vaccinations against diphtheria and poliomyelitis if the family doctors, in the course of their work in the homes and in intimate and confidential contact with the population, had not worked as guarantors and agitators for what the health system offered.

Knowing the circumstances as they are briefly sketched above, it will scarcely come as a surprise to learn that for many years there has been a state of close co-operation between the medical profession and the health authorities. Through the medium of several of its committees the Danish Medical Association takes a direct share in the work of the National Health Service — pursuant to voluntary agreement and in mutual independence.

I am aware that a system of this kind necessitates an adequate number of physicians. At the moment, Denmark has one doctor per 850 of the population, about half of the total being occupied at the hospitals and half in general practice.

LOCAL HEALTH OFFICERS

The local health officers are in charge of the medical-hygienic section of the local health work, including hygienic control of housing, food, etc. Their sphere otherwise as officials under the National Health Service is described in one of the previous articles.

I shall refer here merely to the much debated question of principle: health officers solely, or health officers with access to a private practice.

All Danish health officers have the right to have a practice in so far as their official work permits, and only few refrain from utilizing that right.

Personally, I have always considered it very fortunate for the local health service that health officers do so to a reasonable extent. It gives them the close contact of the G. P. with the population among whom they work. The confidence won by the doctor through the exercise of his profession is transferred to the health officer also when he has to make disagreeable decisions; and — I attach great importance to this — the health officer does not forget his original calling: that of a physician.

In the course of time there has been no lack of invitations to try to change this perhaps rather old-fashioned system. I have declined to help in making any such change — and have had no reason to regret it.

For the same reason it has been a source of satisfaction to me to be able to attach to the staff of physicians in the National Health Service doctors who can devote a few hours daily to clinical work outside the office.

As a last word about our system of local health officers, I may add that the TB-clinical work and workers' protection are attended to by specially trained physicians in collaboration with the medical officers when the hygienic work requires it. This arrangement has proved most useful.

THE DOCTOR'S PLACE IN THE ADMINISTRATION. LAYMAN AND PROFESSIONAL MAN IN THE HEALTH SERVICE

Centralization is inclined to promote officialdom.

Decentralization — tasks and responsibility laid as charges upon the local government body in smaller communal units — appeals to the understanding of the man in the street and is a protection against the possible "dictatorial" tendencies of experts, administrative as well as technical.

It is open to discussion — and in fact is discussed in many places — what is the proper way to obtain the best results for national health: centralization or decentralization. Here again no definite answer can be given. A doctor's position and working conditions in the service of public health will be affected by and depend upon how it is organized. The nature and extent of the non-medically trained staff of assistants will also depend upon the form of organization.

My experience, and the background of my evaluation of it, is based upon conditions in the Danish health service with its widely decentralized administration but with the professional hygienic-medical, chiefly advisory elements centralized in so far as the local health officers work in the service of the Central Administration (the National Health Service).

The hospital system is communal, and public hygiene is in the hands of local committees under the communal councils. Members from the popularly elected councils (county and town) take a direct part in the administration of both hospitals and other organs of the public health system.

Neither the physicians-in-chief at the hospitals nor the local health officers share as such in administration work.

The chief physicians participate in the hospital administration as counsellors on medical matters in the broadest sense of the term.

The local health officer has the supervision of the institutions of public hygiene within his district, and he is a member of the local health committees. Not only through this membership, but in pursuance of the lawful obligations of his office, he is the expert adviser to the communal administrative and finance authorities who must consult him on all sanitary questions.

As far as the hospitals are concerned, I have never had the slightest doubt that the daily ad-

ministrative work there must be in the hands of professionally trained administrators. The younger hospital doctors, at any rate, agree and feel that they have their hands full with the work for their patients and with keeping themselves constantly abreast of their science and art.

The position of the health officer is more open to debate. Many would think it not only natural but most natural for him to be equipped with direct administrative authority beyond his relations with the medical persons. Thus the question is: would he become "strengthened" by it — obtain greater results? As supervisor, with powers of reprimanding, and as professional adviser to the communal council and the administrative organs occupied with public hygiene, the expert authority of his office will place him in a strong position vis-á-vis those communal authorities who have the final responsibility and in many cases besides have to grant the funds. This being so, he will not only be able to achieve with greater powers as much as he could by enforcing his views, but still more. In the capacity of counsellor he will have opportunities — in fact he will be obliged — to try to convince the responsible non-medical communal authorities of the soundness of his opinions. It is open to him to win over the elected members of the council and, in the final instance, large sections of the people who elect them and among whom he works, to gain their confidence and sympathy and their collaboration.

In the course of time I have often been asked the question: Who is the Minister of Health? Where is the Health Department — how can one build up a health service without its own administrative organ with direct administrative powers as in a separate ministry or a separate Health Department?

We have a health system but neither a Health Ministry nor a Health Department, and I don't think anyone in our country has any real motive for wanting a change in that position.

As I have said, the public health work is looked after locally by communal councils and centrally by various ministries, more especially by the Ministry of the Interior, which also supervises the communes, but also by the Ministry of Social Affairs, the Ministry of Agriculture, etc.

In addition, there is a central medical organ (the National Health Service) which, besides superintending the health personnel: doctors, nurses, pharmacists, dentists, midwives, etc. and all the health institutions and health legislation on the whole, works in an advisory capacity with the central administration with powers and obligations to submit proposals for expanding and amending both health laws and administrative decisions.

The central position of the National Health Service, with the closest, statutory contact and co-operation with both the central administration and the communal councils and the local health officers stationed in the various parts of the country, enables it to acquire an intimate knowledge of the health of the country and the various institutions and administrative organs which locally and centrally carry out the multilateral work of the health system.

With this knowledge and with the expert assistance available in the form of a large number of scientifically highly qualified counsellors, and through its advisory and initiating activities, the National Health Service is in a position to get medico-hygienic evaluations and suggestions submitted and respected, besides decisively helping in the co-ordination of all the health work, so that in spite of decentralization there is homogeneity of objects and endeavours.

A health service makes calls upon the physician and the administrator. Some believe it practicable to find physician and administrator in one person with medical qualifications and to build the system on him. Naturally, such individuals do exist, but generally speaking a division of labour between two collaborating parties will give the best results.

A physician will often fail with administrative problems and work in which he has had no training. He will often lack the flexibility provided by special administrative training in the form of wider views and greater familiarity with legislative and administrative customs. Decisions of a medically trained administrator in such cases are liable to be more rigid, more categorical — or, shall we say, doctrinaire. In the hand of a medical administrator the pen is apt to become a dangerous instrument, especially when he discovers its potential power.

On the other hand, the medical man is in a strong position, often impregnably strong, as the professional adviser who, with his qualifications, his knowledge and his insight, can decisively mould the course of developments, its aims and the choice of ways and means.

This of course does not mean that the adviser must be devoid of administrative understanding and sense — on the contrary, just as the non-medically trained administrative collaborator acquires an understanding and knowledge of the medical aspect of the work.

These many years of working under the Danish Health Service have taught me to regard the advisory and initiative part of the collaboration with the administration as a privilege of the highest value, a privilege which, together with the duty and right to advise and guide, gives rich possibilities of moulding developments to the advisor who performs his task on the background of an intimate knowledge of the economic strength and capacity of the community and in contact and sympathy with political life.

The question of "the learned and the unlearned" where public health is concerned is not an "either/or" but a "both/and", requiring

the most intimate and sympathetic co-operation, a co-operation in which the physician must renounce external "power" in order that his insight and medical knowledge may enable him with so much the greater force to bring about the all-important collaboration in arranging aims and organization.

The doctor makes the diagnosis, prescribes the medicine and explains why. The patient himself decides whether to take it or not — but what patient would let it be?

TRAINING

Finally, a few words on the training of local health officers. As far as I can see, there has been a growing tendency for some years to regard the medical service in public health as specialist work, requiring special training.

I agree with that opinion, inasmuch as we must all grant that health officers have tasks which require a special insight into questions of pure hygiene and also into his country's legislation.

Since 1915 the Danish health system has had a statutory rule that no one except physicians who have taken a special course concluding with an examination can be appointed as a health officer.

But from there to the large "public health schools" with their special training, but without the qualification of previous clinical experiences, is a long spring, one that may end in the adoption of a principle with consequences which perhaps may not prove to be best for future developments.

Specialization within the science and practice of medicine is necessary and in constant growth. In the treatment of the sick, however, specialists must still and always will be compelled to work so closely together that the foeling of being a team working for a common purpose can be preserved. It is different with physicians specially trained at schools of hygiene who pass into the service of public health and lose all contact with the science of healing. There is great danger of a schism between them and the clinicians.

My experience of fruitful co-operation with the medical profession and with health officers who feel as workers in that profession — feel themselves physicians, bids me warn against isolated special training in hygiene, epidemiology, etc., without the qualification of a thorough previous clinical training.

On the other hand, it would probably be of vital importance if fundamental training in disease prevention and health preservation could be given medical students together with and in conjunction with their clinical training. This would ensure that all physicians were familiar with that part of a doctor's work.

Special training and continuation courses for doctors who wish to get into or are in the health service can be arranged in schools of hygiene; but a reasonable portion of clinical training must be a condition of participation in such training.

I shall end as I began:

Health as a concept is governed by disease and infirmity. Disease is the origin and basis of all work for health, the work of healing and preventing disease.

It is the doctor, the man who has a doctor's mind who is summoned to the sick bed and to the healthy child who is to be kept healthy, to the operating theatre and to the offices of the health service.

To all with a medical training in the service of public health I would say: go on being doctor-minded; never forget to be a doctor.

FIRST INTERNATIONAL CONGRESS OF HUMAN GENETICS

Copenhagen 1956

The First International Congress of Human Genetics will be held in Copenhagen, Denmark, August 1—6, 1956. The scientific program will comprise plenary sessions, section meetings and scientific exhibitions.

The subjects of the *plenary sessions* are planned to be:

Wednesday, August 1: I. Opening Session. II. Mutation in Man. III. Radiation Genetics and its Human Implications.

Thursday, August 2: I. Quantitative Inheritance in Man. II. Comparative and Experimental Pathology in Relation to Human Genetics. III. Biochemical Genetics in Man.

Friday, August 3: I. Methods in Human Genetics: a. Family Studies. b. Twin Studies.

Saturday, August 4: I. Genetics and Medical Research. II. Medical Applications of Human Genetics.

Monday, August 6: I. Social Applications of Human Genetics. II. Epidemiological Control of Hereditary Diseases: Genetic-Hygienic Registration. Medico-Genetic Ascertainment.

In the *sections* invited and proffered papers will be read. So far 220 papers have been proffered, and 17 sections have been planned.

Enrolment at normal fee (Dan. crowns 150.—) is open until April 1, 1956. After that the fee will be increased by 50 %. Application to read a paper or to exhibit must be forwarded before April 1.

For further information please apply to:

First International Congress of Human Genetics, 14 Tagensvej, Copenhagen N., Denmark.

NEONATAL MENINGITIS

INVESTIGATIONS OF SOURCES AND ROUTES OF INFECTION

By A. DUPONT and E. THAMDRUP

Acute purulent meningitis in the newborn is no rare disease. Cruickshank (10) found 33 cases of meningitis (4 per cent) in a post-mortem material comprising 800 infants dead within the neonatal period (i. e., within the first month of life). Flensborg (18) submitted 674 infants to post-mortem examination (stillborn and dead in the maternity units of the Rigshospital) and found three with meningitis (a scant ½ per cent). This is a minimum figure, the skulls of 186 infants having not been opened.

Neonatal meningitis is often due to bacteria which rarely cause this disease in older age-classes.

Barret et al.'s (3) survey of Bact. coli meningitis shows that out of 104 published cases comprising all age-classes, 63 occurred in infants under 3 months of age. Out of 150 cases of neonatal meningitis collected from the literature by Flensborg in 1943, 50 per cent were caused by coli or coliform bacteria.

In the reports on the age distribution and bacteriological diagnosis in acute purulent meningitis in infancy, neonatal meningitis varies somewhat in frequency, presumably owing to a difference in the kind of patients admitted to the units concerned. Neonatal meningitis is more frequent in paediatric units, which receive many newborn infants, than in isolation units. In a review from 1954 by E. S. Smith (40), comprising 409 cases of meningitis in all age-classes, 36 (9 per cent) occurred among infants in the first month of life. The frequency was not higher in any other month of life. The bacteria responsible for the meningitis were demonstrated in 19 of the 36 cases, being pneumococci in one case and in the remainder gram-negative bacteria, of which there were coli strains in 13.

In addition to the papers mentioned above, reference may be made to the following, in which a fairly large numbers of cases of neonatal meningitis have been collected: Fothergill and Sweet (20) 1933, Craig (9) 1936, Cislaghi (7) 1940, Kagan et al. (25) 1949, Debré and Mozziconacci (11) 1949.

MATERIAL

The series of cases under review comprises nine patients from the Children's Hospital at Martinsvej. In the unit concerned, 11 cases of neonatal meningitis were diagnosed within the period 1945—55. Two were caused by staphylococci and non-haemolytic streptococci, having therefore not been included in the present investigation. Nine (about 80 per cent) were due to gram-negative rods (one, however, a mixed infection of coli bacteria and non-haemolytic streptococci). Two of the cases occurred during the years 1948 and 1949, and seven within the period from 1952 to 1955. The much higher frequency within the last 3 years than during the preceding period may be real, but may, perhaps, also be due to the fact that within the past 3 years lumbar puncture has been performed at much wider indications on the newborn, owing to two cases having occurred within one month.

Table 1.
Cerebrospinal fluid findings in 9 patients with neonatal meningitis caused by gram-negative rods (however, in one case mixed infection with coli bacteria and non-haemolytic streptococci).

Pt. no.	Cell count	Bacteriological findings	
		Dir. Micr.	Culture
1	Innumerable leucocytes	G- rods	Coli
2	No count „Macroscopically purulent"	G- rods	Coli
3	Thick pus	G- rods	Coli
4	Blood-stained C.S.F. More leucoc. than accountable for by blood admixture	G- rods	Coli
5	Blood-stained C.S.F. 150/3 leucoc. 1500/3 erythr.	G+ cocci	Non haem. streptococci Coli
6	No count Blood-stained C.S.F.	no bacteria	Atypical Klebsiella
7	40,000/3 leucocytes	G- rods	Coli
8	12,800/3 leucocytes	G- rods	Coli
9	Innumerable leucocytes	G- rods	Coli

Table 1 shows the results of C. S. F. analyses. A diagnosis of purulent meningitis could at once be established in six cases on the basis of the cell count, but only a small quantity of blood-stained

From the Children's Hospital at Martinsvej (Chief: *E. Winge Flensborg*) and the Statens Seruminstitut (Director: *J. Ørskov*).

cerebrospinal fluid was obtained from patients Nos. 4, 5, and 6. The cell count in Nos. 4 and 5 gave a somewhat greater number of white blood cells than was accountable for by the admixture of blood. In patient No. 6 the admixture of blood was so pronounced as to make a count impossible. The bacteria responsible for the meningitis were demonstrated by direct microscopy of the cerebrospinal fluid in all cases, except in this one, and in No. 5, in which latter direct microscopy revealed only gram-positive cocci, while a culture showed coli bacteria as well.

SYMPTOMS

The signs and symptoms of the nine patients have been set out in Table 2. The diagnosis was made between the third and the ninth day of life. It is remarkable that three of the patients had had no temperature rise. One patient lay in opisthotonus position, whereas none of the remaining eight displayed neck and back rigidity. The fontanelle showed increased tension in three, or perhaps five, but was of normal tension in four. In three cases, those with the tense fontanelle, the extremities seemed rigid. Twitchings, convulsions, or tremor were seen in six cases, strabismus or nystagmus in four, palsies in two, cyanosis or change of colour in six. They were all reluctant to suck, and three vomited or regurgitated more than normally.

A view of the symptoms of the individual patients shows a remarkably symptomless course of the infection in some cases, particularly the latter three. No. 9 presented change of colour in addition to the slight temperature rise and reluctance to feed, No. 8 a temperature rise, reluctance to feed, and mild strabismus, and No. 7 the same as No. 9. None of these three patients presented features suggesting meningitis, except that No. 7 had a doubtfully tense fontanelle. It is worth noting, however, that all our nine patients had at least one clinical feature pointing towards a possible cerebral affection, in the least pronounced cases change of colour or strabismus.

The uncharacteristic clinical picture has been pointed out by several writers (Craig (9), Flensborg (18), Fraser (21)). Craig and Fraser state that in some instances we see no other symptoms than reluctance to feed, general faintness, and poor thriving.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis we must consider any condition that may involve debility in the neonatal period, but in particular infections and conditions associated with cerebral symptoms: Affections due to birth injury, tetanus neonatorum, and neonatal tetany. Cerebral haemorrhage occurs in some cases in association with the meningitis (Lindberg (32), Rydberg (39)). Spinal puncture revealed signs of cerebral haemorrhage in three of our patients (Nos. 4, 5, and 6). In Nos. 5 and 6 the diagnosis was confirmed at necropsy. As pointed out by Fraser (21), it may in some cases be impossible to make a diagnosis of meningitis by counting the white blood cells in the cerebrospinal fluid when this is full of blood. In such cases culture of C. S. F. specimens should be carried out and antibacterial treatment instituted.

Bojlén (5) has described a case that was indistinguishable from tetanus neonatorum. The diagnosis could only be established post mortem.

The uncharacteristic clinical picture no doubt explains why so many cases are not diagnosed till after death. If a bacterial post-mortem examination is not performed, a number of cases will not even be recognised at autopsy, especially not cases where cerebral haemorrhage is the direct cause of death. C. F. S. analysis being necessary for establishment of the diagnosis, lumbar puncture should be performed at wide indications, such as we have carried through the past 3 years. The number of cases of meningitis observed within this period seems to us to justify this procedure, which was also advocated by Flensborg (18) in 1943 and Fraser (21) in 1952). We have seen no complications following the punctures (e. g., shock, secondary cerebral haemorrhage, wedging of the cerebellum or brain stem in the foramen magnum). Five patients died, all within 36 hours of the puncture, but four of these were in a very bad state prior to the puncture. At necropsy two were found to have cerebral haemorrhage, which had also been diagnosed before death by spinal puncture. None showed wedging. The puncture should be performed cautiously, using a thin cannula with a syringe attached for suction of a possibly thick purulent cerebrospinal fluid, and the amount of fluid withdrawn should be small. If one hesitates owing to the risk of wedging, puncture can be performed instead laterally in the fontanelle, as we do when examining a patient for suspicious subdural hygroma. The differential diagnosis, and especially early diagnosis, are important now that the prognosis, thanks to sulphonamides and antibiotics, is no longer hopeless.

COURSE AND TREATMENT

Table 2 shows that five of the nine patients died, all within 36 hours of the institution of treatment. The remaining four recovered, but two, Nos. 3 and 8, developed hydrocephalus, which was treated neurosurgically, in one case by ventriculoperitoneostomy and in the other by ventriculo-ureterostomy. Both patients are mentally defective and one also spastic. Patients Nos. 1 and 9 recovered without defects. No. 1 was observed for 6½ years and No. 9 for 6 months.

The five dead patients died so soon after the treatment had been started that we had no chance of evaluating its effect. The treatment here consisted in blood transfusions, in addition to chemo-

Signs prior to lumbar puncture in nine patients with cerebrospinal meningitis. In all cases the disease was recognised between the third and the fifth day of hospitalisation.

Pt. no.	Sex	Date of puncture	Neck or back rigidity	Tense fontanelle	Petechiae	fever (highest) (tmp. C.)	Rigidity
1	boy	9th day of life	÷	(+)	÷	39.2	÷
2	girl	8th day of life	÷	÷	÷	39.1	—
3	girl	8th day of life	+ (opisthotonus)	+	÷	38.7	+
4	boy	3rd day of life	÷	+	÷	—	+
5	girl	5th day of life	÷	÷	÷	—	÷
6	boy	3rd day of life	÷	+	+	—	+
7	boy	8th day of life	÷	(+)	÷	38.9	÷
8	boy	4th day of life	÷	÷	÷	38.2	÷
9	boy	8th day of life	÷	÷	÷	38.2	÷

therapy and antibiotic treatment. The chemotherapy and antibiotic treatment of the four survivors appears from Table 3. Streptomycin and penicillin were injected i. m., while the other drugs were given by mouth or as rectal suppositories. Resistance tests of the coli strains found in the four survivors, using the tablet method (Lund et al. (33)), showed the following facts:

Sensitivity to penicillin: 0, sulphonamides: ++, streptomycin: +++, Aureomycin: ++, chloramphenicol: +++, and Terramycin: +++.

In one case (No. 8) a change occurred during the sterptomycin treatment, the sensitivity to streptomycin having fallen to 0 in the course of 5 days.

The treatment was most effective in patient No. 9, whose cerebrospinal fluid was sterile after 48 hours with streptomycin and chloramphenicol and 24 hours with Na-penicillin. In patient No. 1 coli bacteria were still recovered from the cerebrospinal fluid after 6 days of treatment (penicillin and sulphathiazole), whereas on the ninth day the fluid was sterile. In patient No. 3 coli bacteria were recovered from the cerebrospinal fluid after 5 days of treatment with streptomycin and chloramphenicol, but after 10 days the fluid was sterile. In patient No. 8 the cerebrospinal fluid did not become sterile till after 30 days of treatment alternately with antibiotics and chemotherapeutic agents. The first sterile C. F. S. specimens were obtained after 6 days of treatment with Na-penicillin in large doses (500,000 units b. i. d.) and alphasol. As treatment with sulphonamide had previously been tried in the form of lucosil (sulphametizole), there is reason to suppose that the large doses of Na-penicillin had decisive effect, in spite of the resistance of coli bacteria to penicillin demonstrated by ordinary resistance test (cf. Riewerts-Eriksen's (16) examinations of penicillin-resistant staphylococci).

A subdural hygroma (Burlington et al. (6)) might have been suspected as the cause of the protracted course of the disease in this patient, but a hygroma was not found by subdural puncture.

PROGNOSIS

The prognosis was practically hopeless prior to the introduction of sulphonamides and antibiotics in the treatment. Reports are available on five cured cases before this time (19, 23, 30, 36). Four of these infants developed hydrocephalus, while we have no information on the fifth infant's condition after the cure of the meningitis. The infant had spina bifida. By reviewing the literature we have found altogether 24 cured cases (3, 4, 12, 15, 17, 19, 21, 22, 23, 25, 30, 31, 34, 36, 38, 40, 42, 43). In six cases we have no information on the observation period, nor as to whether the meningitis had caused permanent cerebral damage. 12 patients are reported to have recovered completely and 6 to have developed hydrocephalus.

Most of the patients have been treated with several antibacterial drugs. A small number, however, have been cured with sulphonamide or streptomycin alone or combined with chloram-

...tal meningitis due to gram-negative rods. The ... day of life. Five patients died, all within 36 ...nosis.

Twitchings and convulsions	Strabismus or nystagmus	Palsies	change of colour	reluctant to feed	vomiting regurgitation	death	late prognosis
(+)	÷	÷	÷	+	÷	—	norm. child obs. period $6^1/_2$ years
+	+	+ lt. upper extr.	+	+	+	+	
+	+	÷	+ (cyanosis)	+	+	—	hydrocephalus obligopcrenia spasticity
+	÷	+ facial	÷	+	?	+	
+	÷	÷	+	+	+	+	
(+) tremor	+	÷	+	+	?	+	
÷	÷	÷	+	+	+	+	hydrocephalus obligophrenia
÷	+	÷	÷	+	÷	—	Norm. child obs. period 6 mths.
÷	÷	÷	+	+	÷	—	

phenicol. According to the results of resistance tests, these substances must also be expected to be the most active. According to our own experiences and the data stated in the literature, a combination of sulphonamide, streptomycin, and chloramphenicol must be the most rational treatment of Bact. coli meningitis. If coli bacteria are still present in the cerebrospinal fluid after 2 or 3 days of treatment, we suggest Na-penicillin in very large doses (500,000 units b. i. d.). We have not tried intrathecal treatment, but in the literature we find eight cases given streptomycin intrathecally (4, 12, 15, 21, 22, 42, 43) and one given chloramphenicol (17). All these patients are stated to have recovered completely, but only three have been observed for a fairly long time. If the patient does not respond satisfactorily to the treatment (bacteria still present in the cerebrospinal fluid, incomplete temperature fall or secondary temperature rise, persisting vomiting, failing gain in weight, neurological or ocular signs that do not subside), the patient should be examined for subdural hygroma.

PATHOGENESIS

The low resistance of the newborn to infections, due especially to the absence of coli agglutinin in the blood, has been stated as the cause that otherwise not very pathogenic bacteria provoke meningitis in such a great number of newborn (Adamson, Löfgren, and Malmnäs (1)). The disease is particularly frequent among prematures (40 per cent of the infants in Cruickshank's series and 71 per cent of those in Craig's series were prematures). Cerebral haemorrhage may, perhaps, also play a pathogenic part in certain cases, the bleeding producing a locus minoris resistentiae, where the infection settles.

In some cases of neonatal meningitis there is found an extrameningeal focus from which the infection has proceeded: Cutaneous and mucosal infections, umbilical infections, pyuria, otitis, pneumonia, enteritis.

In a few cases of Bact. coli meningitis in the newborn a Bact. coli infection was demonstrated in the mother: Pyelitis (Attenstaedt (2) 1933, Moncrieff (35) 1953), pyelitis and endometritis (Duval and Burrowes (14) 1948). Intra-uterine transmission of the bacteria has been a subject for discussion. Aspiration of infected liquor amnii or infected bath water has been suggested as a possible cause.

However, in the majority of cases no infection is demonstrated in the mother, nor any focal extra-meningeal focus in the child.

In many instances sepsis has been found in the child, either by blood culture (Fothergill and Sweet (20), Debré (12), Craig (9)), or demonstrated patho-anatomically or by culture at necropsy (Cruickshank (10)).

Present Investigations:

The courses of the parturition and puerperium in the nine cases under review are seen in Table 4. Two infants weighed under 2500 g at birth. In three cases the liquor amnii had escaped 24 hours before birth and in one case 12 hours before. In three cases the hour of escape could not be elucidated. In two cases the parturition lasted

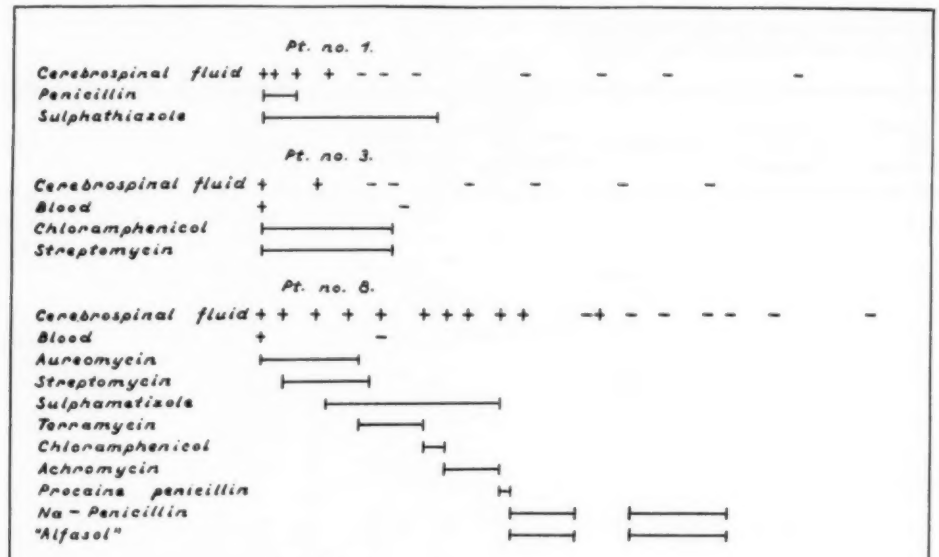

Table 3.
Cultures of cerebrospinal fluid and blood in relation to antibacterial treatment in four patients cured of neonatal Bact. coli meningitis.

Table 4.
Course of the parturition and the infant's condition immediately after birth. Signs of puerperal infection in the mother.

Pt. no.	Duration of parturition in hours	Escape of liquor amnii hours before parturition	Complications of delivery	Child's condition at birth	Birth weight (g)	Mother: temperature rise	Mother: purulent vag.discharge post part.
1	15	1	÷	good	3.200	÷	÷
2	2	?	Part. plac. praevia. Prolapse of umbilical cord. Version. Extraction.	Asphyxial 2nd degree	2.600	?	?
3	10	24	Rupture of the membrane. Vag. exploration. Delivery by forceps.	Asphyxial 1st degree	2.600	+	+
4	12	?	Episiotomy Expression	Asphyxial 2nd degree	3.100	÷	÷
5	18	?	÷	good	1.970	?	?
6	36	24	twin birth	good	2.900	÷	÷
7	8	1	÷	good	2.000	÷	÷
8	29	24	÷	good	3.200	÷	÷
9	5—6	12	÷	cyanotic	3.500	÷	÷

Table 5.
Results of bacteriological examinations of specimens from mother and infant.

Pt. no.	Bacterium	Child							Mother
		C.S.F.	Blood (marrow)	Nose	Fauces	Faeces	Umbilicus	Post mortem examination	
3	E. coli 0 group 18	+	+	+	÷	÷	not exam.	pt. recovered	+ vagina
4	E. coli 0 group 18	+	+	+	+	+	+	+	+ urin faeces
5	E. coli 0 group 4	+	+	not exam.	not exam.	not exam.	not exam.	+	not exam.
6	Atypical Klebsiella	+	+	+	+	+	÷	+	÷
7	E. coli 0 group 4	+	+	+	+	+	÷	+	÷
8	E. coli, very rough	+	+	+	+	+	not exam.	pt. recovered	÷
9	E. coli, very rough	+	+	+	+	+	+	pt. recovered	÷

*) We wish to thank Dr. Fritz Ørskov for the serological diagnosis.

over 24 hours, and in three it was complicated. Early escape of the liquor amnii, protracted and complicated parturition, involving intervention, increase the chance of infection of the birth passages and consequently infection of the child. Five of the infants were in good condition at birth, while three were asphyxial, and one cyanotic. One of the mothers had a raised temperature during the puerperium and purulent lochia. In two cases we do not know the course of the puerperium.

The infants were examined clinically with a view to tracing a focal infection outside the meninges (skin, mucous membranes, ears, lungs, urine). An extra-meningeal focus was demonstrated in one patient only (No. 7). It was a bilateral otitis media caused by coli bacteria.

BACTERIOLOGICAL EXAMINATIONS

In 1922 Cooke and Bell (8) entertained the idea that certain coli groups are particularly associated with meningitis in the newborn.

Owing to the lack of a serviceable serological classification and of a uniform nomenclature, it is impossible to decide whether the microorganisms in the previously published cases had common properties. A more uniform basis for comparison has been obtained since the appearance of Kauffmann's and his collaborators' works on Bact. coli serology and Bact. coli diagnosis (Kauffmann (26) 1943 and (27) 1944, Knipschildt (29) 1945. In 1951 Laurell et al. (31) reported a case of neonatal meningitis caused by E. coli bacteria, which were examined serologically and biochemically according to these modern methods. This strain could not be classified in any known group, nor is it identical with any of the strains found in our cases. The interest displayed in E. coli in infants, especially in infants with diarrhoea, has given rise within recent years to a great number of works dealing particularly with special E. coli groups (0 111:B4, 0 55:B5, 0 26:B6), these groups being supposed to be of aetiological importance in infantile diarrhoea. In connection with these investigations a few cases have been reported of meningitis in infants caused by the stated E. coli groups (Drimmer, Hernnheisser, and Olitzki (13), Smith, Galloway, and Speirs (41), Neter (37).

Present Investigations:

Typing was performed of the gram-negative rods found in the last seven of our patients. In six cases nasal and faucial swabs were taken from the infant and the mother, as well as specimens of stool and blood or bone marrow, the infant's umbilicus, the mother's vagina and catheterised urine immediately on demonstration of infected cerebrospinal fluid, before antibacterial treatment was instituted. These specimens were cultured aerobically and anaerobically in liquid medium and on plates for ordinary bacteriological analyses. Possibly occurring colonies of gram-negative rods were compared with the micro-organisms found in the cerebrospinal fluid.

In a single case (No. 8) nasal and faucial swabs from the mother's co-patients and the staff of the maternity unit were also examined for the same micro-organisms, but with a negative result throughout.

Four dead patients were submitted to bacteriological post-mortem examination.

Table 5 shows the bacteria found in the cerebrospinal fluid. They were E. coli in six cases and an atypical Klebsiella in one. The table states whether the same bacterial type as demonstrated in the cerebrospinal fluid was found in specimens from the infant, on bacterial post-mortem examination, and in specimens from the mother. It is

Table 6.
The biochemical properties of the gram-negative rods found in the last seven patients with neonatal meningitis.

Patient no.	3	4	5	6	7	8	9
Adonitol	—	—	—	—	—	—	—
Dulcitol	$+^{2}$	$+^{2}$	$+^{2}$	—	$+^{2}$	—	—
Sorbitol	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$
Arabinose	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$
Xylose	$+^{1}$	$+^{1}$	$+^{7}-$	$+^{1}$	—	$+^{1}$	—
Rhamnose	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$
Maltose	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	$+^{1}$	—	$+^{1}$
Salicin	$+^{3}$	$+^{3}$	$+^{1-2}$	$+^{1}$	$+^{2}$	—	$+^{8}$
Inositol	—	—	—	$+^{2}$	—	—	—
Lactose	$+^{1}$	$+^{1}$	$+^{2-7}$	$+^{3}$	$+^{1}$	$+^{1}$	$+^{1}$
Sucrose	—	—	—	$+^{1}$	—	$+^{1}$	—
Mannitol	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L
Glucose	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L	$+^{1\,1}$ L
Indole	$+^{1}$	$+^{1}$	$+^{1}$	—	$+^{1}$	$+^{1}$	$+^{1}$
H_2S	—	—	—	—	—	—	—
Gelatine	—	—	—	$+^{30\ 60}$	—	—	—
Ammonium-glucose	+	+	+	+	+	+	+
Ammonium-citrate	—	—	—	+	—	—	—
Nitrite reduktion KNO_3	+	+	+	+	+	+	+
Voges-Proskauer	—	—	—	+	—	—	—
Methyl red	+	+	+	—	+	+	+
Urea	—	—	—	—	—	—	—
Motility	slight	slight	+	+	+	+	+

Symbols: $+^{1}$ = acid production after 24 hours.
$+^{2-3}$ = acid production after 2—3 days.
— = no reaction within 30 days (gelatine observed for 3 months).
+ 'L' = acid and gas after 24 hours.
indole — = no reaction, tried after 24 and 48 hours.
+ = positive reaction according to the rules for the technique employed — vide F. Kauffmann »Enterobacteriacea« (28).

seen that in all cases the bacterium noticed in the cerebrospinal fluid was discovered from blood and from nasal and faucial swabs, in five out of six cases from faecal specimens, and in two out of four from umbilical specimens. Patient No. 7 had bilateral otitis, from which coli bacteria were isolated. Unfortunately these were not typed; but the same coli type as was responsible for the meningitis was discovered from the infant's blood, fauces, and nose. In the patients submitted to autopsy the same bacterium as demonstrated in the cerebrospinal fluid ante mortem was discovered from blood and internal organs post mortem.

In two cases the specimens taken from the mothers were found to contain the same bacterial type as the infant's cerebrospinal fluid: in the case of No. 8 in the mother's vagina, and in that

of No. 4 in the mother's catheterised urine and faeces.

Table 6 shows the results of the biochemical analyses. In the patients Nos. 3 and 4 the E. coli found were identical both biochemically and serologically. These cases occurred within one month in the same hospital, but in different wards. In the remaining five cases, gram-negative rods were demonstrated with no serological or biochemical relationship. The patients Nos. 5 and 7 were both infected with E. coli belonging to O group 4, but the 2 strains were not identical, overlapping having been ascertained to other widely differing O groups.

In no more than one of the seven cases was it possible to follow the infant's seroreaction, the infant having survived an infection with a mild strain. The infant, No. 3, had blood samples taken 21 and 88 days after the onset of the disease. Both samples gave O agglutination up to a serum dilution of 1:128 with own type (E. coli O group 18), but no reaction with controls: O group 1 and O group 55.

CONCLUSION

In two out of six examined cases the bacteriological examinations gave evidence to suggest that the infant's infection originated from the mother: In patient No. 3 from the mother's birth passages, which must be supposed to have become infected during the complicated parturition, and in patient No. 4 from the mother's urine or faeces.

A local extrameningeal infection was demonstrated in one case only (otitis in No. 7). Sepsis was present in all patients. The portal of entry of the infection may have been the nose and fauces, where the pathogenic bacterium was found in all cases, or the umbilicus, where the bacterium was demonstrated in two of four examined cases. Infection direct from the intestinal canal to the blood is also a theoretical possibility.

The hypothesis that certain coli groups are of special aetiological importance for neonatal meningitis has not been borne out through our investigations. The same gram-negative rod was found in only two out of seven cases, and these two could be regarded as epidemically related, having occurred in the same maternity unit within one month.

SUMMARY

A survey is given of the symptomatology, differential diagnosis, treatment, and prognosis of neonatal meningitis on the basis of a series of nine cases caused by gram-negative rods. In addition, bacteriological examinations have been made to throw light on sources and routes of infection.

The uncharacteristic clinical picture is pointed out. Temperature rise, neck rigidity, and tense fontanelle occur in a minority of cases. Lumbar or fontanellar puncture ought therefore to be performed at wide indications in newborn, especially in prematures with signs of cerebral irritation or merely unsatisfactory gain in weight and reluctance to feed. Early diagnosis is important, the prognosis being no longer hopeless since the introduction of antibiotic and chemotherapeutic treatment of the disease.

Neonatal Bact. coli meningitis was followed by hydrocephalus in more than half of the cured cases published with an observation period over 3 months.

Four of our cases were cured. Two of the patients developed hydrocephalus, while the two others recovered completely with no cerebral sequelae; one was observed for 6½ years and the other for 6 months.

It is concluded that the most effective treatment is a combination of sulphonamide, streptomycin, and chloramphenicol. If the cerebrospinal fluid is not sterile after a couple of days, Na-penicillin in large doses is recommended, treatment with this drug having been found effective in one of our patients who had responded to no other treatment. Streptomycin and chloramphenicol ought, perhaps, to be injected intrathecally.

In six cases we cultured nasal and faucial swabs and faecal specimens from mother and child, as well as specimens of the child's umbilicus and bone marrow, and of the mother's blood, vagina, and urine, in an attempt to throw light on the sources and routes of infection. The same bacterial type as was present in the infant's cerebrospinal fluid was in all cases demonstrated in the infant's blood as well as nose and fauces, in most cases in the faeces, and in half of the cases in the umbilicus; further, in one case in the mother's vagina, and in another in the mother's urine and faeces.

Two cases were caused by the same bacterial type, but these can be regarded as epidemically related, having occurred within one month in the same maternity unit. The remaining cases were caused by different gram-negative rods.

One patient had otitis media caused by coli bacteria. None of the other patients presented an extrameningeal inflammatory focus.

Four of the dead patients were submitted to bacteriological post-mortem examinations. The same bacterial type as was demonstrated ante mortem was in all cases discovered from blood and internal organs post mortem.

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INFANTILE CORTICAL HYPEROSTOSIS

(CAFFEY'S SYNDROME)

By JØRGEN KRINGELBACH

Infantile cortical hyperostosis (ICH) is a disorder occurring in early infancy and characterized by 1) a sudden tender swelling of soft tissue in the head, thorax or extremities, 2) hyperirritability, and 3) roentgenologically demonstrable periosteal new bone formation in the bones underlying the soft-tissue swelling.

In a study from 1939 on roentgenological changes in children suffering from bone syphilis (3) Caffey described a patient with multiple cortical hyperostoses of the ribs, clavicles and bones of the extremities; he pointed out that the symptoms of this patient did not fit into any known syndrome, especially not syphilis or scurvy.

In 1945 Caffey & Silverman (4) presented a preliminary report on a new syndrome, which they called ICH. Besides the above patient from 1939 they described three other children, all of them a few months old, who showed similar roentgenological bone changes and a uniform clinical picture.

Shortly afterwards Smyth and associates reported from California seven cases of "Periosteal reaction, fever and irritability in young infants. A new syndrome?" (15), and during the following years records of individual cases of this syndrome appeared from many different places (1, 2, 5, 8, 9, 10, 11, 13, 16). One of the latest and

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most comprehensive descriptions was published by Sidbury & Sidbury (14), who added 10 cases to the about 60 previously reported.

The disorder, designated in Anglo-American literature as Caffey's or Caffey-Smyth's syndrome, seems to have been described with certainty only once before 1939 (12).

So far, no case has been reported from Scandinavia.

Occurrence, symptomatology, course, and prognosis: The disorder affects only young infants. On an average, the age of onset is 9 or 10 weeks; the disease may, however, occur prior to birth (1) and, in some instances, has set in as late as 5 or 6 months after birth.

Common to the patients are the three above-mentioned symptoms: irritability, soft-tissue swelling and cortical thickening of underlying bones.

The soft-tissue swelling develops suddenly. It is a firm, painful and tender swelling, most often pallid, never erythematous or very hot. It always appears before the occurrence of demonstrable bone changes, and always disappears long before the hyperostoses. Suppuration is never observed. A characteristic of the disease is the fluctuating course: the soft-tissue swelling appears and subsides spontaneously, and it may recur in loco or at other sites.

The skeletal changes, i. e., the cortical hyperostoses, are never found in the epiphyses, but are always restricted to the diaphyses. The most frequent locations are the mandible, and next the tibiae, ulnae, clavicles, and ribs. The below table (from Sidbury & Sidbury) shows the locations in 69 cases, expressed in percentages:

Mandibula	77	per cent
Tibia	44	"
Ulna	36	"
Clavicula	35	"
Costae	32	"
Femur	32	"
Humerus	32	"
Fibula	18	"
Pelvis	6	"
Theca	3	"

Besides the said three characteristics of the disease, the following manifestations are found with somewhat varying frequency: fever, pseudoparesis due to pain, and (in the case of costal involvement) pleural reactions.

The sedimentation rate is increased, and the same applies to alkaline phosphatases. As a rule, anemia is observed, while leucocytosis is often and eosinophilia sometimes found.

So far, serological tests for bacterial and viral infections have all been negative; likewise, inoculation and cultivation experiments have hitherto proved resultless.

The duration of the disease varies from a few weeks to several months; in a few cases manifestations have been found to persist for about two years (6). The spontaneous remissions and exacerbations are characteristic features of the course of the disorder.

The prognosis is good. The children recover completely without sequelae. In a few cases of the disease, however, death from intercurrent infections has occurred (10, 16).

Differential diagnosis: The varying site and extent of the soft-tissue swellings and skeletal changes in the different cases have occasioned a number of differential-diagnostic conjectures: parotitis (the frequently occurring swelling over the mandible), osteomyelitis, syphilis, scurvy, tuberculosis, sarcoma, leucemia, poliomyelitis (pseudoparesis), meningitis, febris rheumatica, traumata (ossificated periosteal haematoma), A-hypervitaminosis, and allergy (the sudden soft-tissue swelling resembling angioneurotic edema).

As far as can be seen, the *etiology and pathogenesis* are still unsolved problems. Owing to the frequent occurrence of fever, elevated sedimentation rate and leucocytosis, it has been considered most probable that ICH was of infectious origin. However, as stated above, all attempts at detecting an infective agent have so far proved futile; further, sulfa drugs, penicillin, streptomycin, Aureomycin, and similar preparations have all appeared to be of no therapeutic effect. Treatment with antihistamines has also turned out negative (13), and it has not been possible to detect any allergens.

Endocrine disorders, infections and intoxication during pregnancy, birth complications, prematurity, and nutritional disturbances (deficiency diseases) may all, according to the facts hitherto revealed, be satisfactorily ruled out as etiological factors.

The occurrence of the disorder in brothers and sisters and familially points to a genetic factor (16); the fact that ICH has been observed in fetuses has led a few authors to explain the disease as a result of an embryonal dysosteogenesis (1).

As regards the *pathologico-anatomical picture*, rather few and somewhat varying descriptions have appeared. The periosteum is found edematous and hyperplastic, easily separable from the underlying thickened cortex, which shows an irregular contour. The bone tissue is poorly vascularized and incompletely structured with defective Havers's canals. The surrounding tissue is involved in the process, and the arteries of the overlying soft tissue and the periosteum show intimal proliferation.

Sidbury considers the arterial changes to be the essential of the process. The resulting hypoxia produces edema with hyperplasia of the periosteum, which in its turn is followed by overproduction of incomplete bone. The arterial intimal proliferation is held to be an inherited defect.

Treatment: In several cases blood transfusions seem to have produced an effect. As mentioned above, treatment with the antibiotics and sulfa preparations hitherto known has proved negative. A few cases have been treated with ACTH and cortisone — apparently with good effect (2, 14); however, owing to the spontaneous healing tendency and the incalculable, fluctuating course of the disease, an evaluation of the effectiveness of drugs employed must, of course, be attended with uncertainty, as long as it is based on individual cases. Still, it must be considered reasonable to try ACTH and cortisone therapy in new cases of ICH.

There is no doubt that ICH is a disorder occurring with a regular increasing frequency. That this increase is not just a reflection of the interest aroused by Caffey's and later Smyth's reports, has been shown by a checking of roentgenograms taken before 1945; the said films revealed very few cases.

Since, as far as the author has been able to ascertain, no case of ICH has been reported from Scandinavia so far, the following case record may be assumed to be of interest.

CASE HISTORY

The patient is a boy aged 4½ months, the second of three children, twin A of dichorial twins. The parents are in good health; especially, the mother was well during the pregnancy. She has received a comprehensive, sufficient diet with supplementary Fe, Ca and Vitamins A and D. The patient was delivered in an uneventful twin birth about two weeks before the expected time.

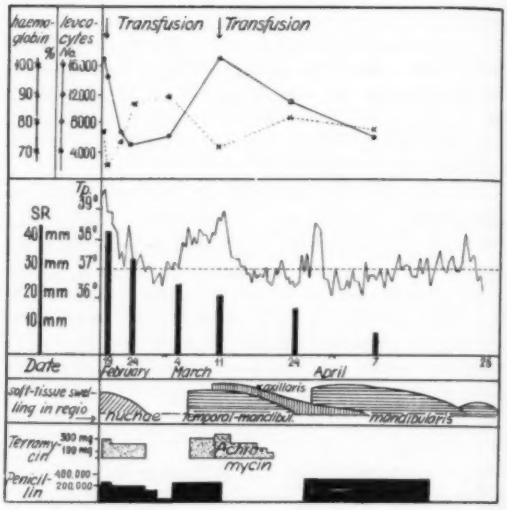
The patient's birth weight was 2700 g, his length 51 cm. Since birth he has thrived well, developed normally and been in perfect health. He has been given an artificial milk diet in accordance with the normal scheme, and has started on supplements of potato and other vegetable mash. He has received an additional supply of Vitamins A, D and C in the normal quantities.

Present illness: 8 days prior to his admission to the children's department the patient became restless, cross and irritable. 3 days later a tender swelling was found in the right axilla. He was febrile, lay with his right leg flexed at knee and hip, and cried at attempts at extending the leg. No special therapy was given. 3 days later the patient was admitted to the surgical department. Examination revealed a flat, tender, not fluctuating swelling laterally and inferior to the right scapula and extending into the right axilla. The following day a slight swelling was noticed in the left parietal region. During penicillin treatment the temperature rose to 40° C. On Feb. 19, 1954, the patient was transferred to the children's department.

He was then in high fever, crying and discontented, but not weak. He was tender to touch, particularly the head, where a tender, pasty-edematous, pallid swelling was observed in the parietal-occipital region. The occipital glandules were found to be firm and the size of peas. The axillary swelling was no more to be seen. The extremities were free. There was moderate stiffness of the neck, doubtful stiffness of the back. The spinal fluid was crystal-clear, 4/3 cells.

The diagnosis was uncertain, and as he appeared to be somewhat weaker the following day, a blood transfusion was given, and at the same time the penicillin treatment was supplemented with Terramycin administration.

The further course of the disease and the essential therapeutic data appear from the diagram.



Curves indicating temperature, micro-sedimentation rate, no. of leucocytes, and haemoglobin; further the variation in the soft-tissue swelling, and the treatment. — Note the rapid fall in temperature and no. of leucocytes after transfusions; later spontaneous falls in temperature are seen.

In the course of the first 10 days the temperature dropped to normal, the swelling in the head disappeared, and Terramycin/penicillin therapy was discontinued, but as X-ray examination now led to the diagnosis "osteomyelitis costae VII—IX dxt.", treatment with penicillin was resumed.

During this treatment the temperature rose; a soft-tissue swelling appeared in the right temporal-parotic-mandibular region. The diagnosis parotitis was considered, but the swelling was not quite in conformity with the picture of that disease. Terramycin was again administered, but 5 days later a palm-size swelling appeared in the lower posterior part of the right axilla. As was the case with the previous swellings, there was no reddening of the skin, nor any fluctuation. The temperature increased; a new blood transfusion was given, and Achromycin was substituted for penicillin/Terramycin. There was a decrease in temperature, and the swelling and tenderness abated. After 9 days Achromycin was discontinued.

5 or 6 days later a conspicuous swelling was again observed over the right mandible. Penicillin therapy was resumed and continued for 3 weeks. During the penicillin treatment there was at first a rise in the temperature, lasting for some days, while later the temperature was normal. The swelling gradually subsided.

Since admission, the sedimentation rate, quite independently of the temperature and the soft-tissue swelling, had been constantly on the decline and at

Table 1.
Blood examinations.

Date	Hb%	Erythr.	Leuc.	Thromb.	Segment.	Stab cells	Eosin-oph.	Basoph.	Monoc.	Lymph.
Febr. 19	78	—	16,600	—	32	23	0	0	16	29
Febr. 20	65	2.8	14,400	368,000	25	36	0	0	10	29
Febr. 22	73	3.9	7,000	202,000	48	0	7	0	12	33
Febr. 24	87	—	4,800	—	13	1	6	1	22	57
March 2	89	5,1	6,450	272,000	24	3	2	0	7	64
March 11	71	4.0	17,000	171,000	33	15	3	0	20	29
March 23	83	4.7	10,800	200,000	26	0	2	0	6	66
April 7	78	4.8	6,100	196,000	14	3	5	1	13	64

last became normal. The general condition was good, and the patient's irritability diminished with the swelling.

A few days after discontinuance of the penicillin therapy there was a new rise in the temperature, which was, however, soon followed by a spontaneous fall and the boy was discharged for his home after well over 9 weeks' hospital residence.

1 month later he was seen for ambulant control. All was well, no new swellings, no fever, normal sedimentation rate.

1 year later: good health, normal thriving and development, no relapses. Objectively: a healthy child, nothing abnormal to be observed.

Examinations: Temperature, sedimentation rate, Hb percentage, and leucocyte count: see the diagram.

Weight 7.6—8.4 kg, height 66—73 cm. (1 year later: 13 kg, 90 cm.). Venular blood: no growth. Bone-marrow: no growth. Staphylococcus antitoxin titre normal (< 2). Wassermann reaction negative. Moro's test negative.

Urine: nothing abnormal. Blood urea 14 mg%.

Blood examinations: see Table 1.

Bone marrow examinations of Feb. 20 and March 11 both showed: erythrocyte diameter: between 3 and 7, moderate anisochromia and polychromasia. The erythropoietic system was normoblastic and showed a shift to the left. No megaloblasts were present. The number of thrombocytes was rather large. In the myelocyte system a marked shift to the left was observed within the neutrophile forms. No atypical cell forms were found. There were no signs of leukemia. In the leucocyte system of the peripheral blood there was a pronounced shift to the left. Immature cell forms were not observed in the peripheral blood. The monocyte percentage (March 11) was increased. The picture showed a distinct reactive change. (Søeborg-Ohlsen).

Roentgen report: Feb. 20. Cranium: swelling of soft tissue, most marked in the parietal-occipital region. No osseous abnormality. Lungs: doubtful infiltration (partial atelectasis?) of the right basal lobe. March 1. Thorax: 7th, 8th and 9th costae dxt. considerably thickened. There seem to be marked periosteal thickenings around these bones, extending their entire length. Diagnosis: osteomyelitis costarum. Cranium: no soft-tissue swelling, no certain osseous abnormality. March 10. Cranium: nothing abnormal. Thorax: swelling of soft tissue in the right axilla. Costae unchanged. Lungs normal. March 23. Cranium: nothing abnormal. Thorax: costal processes healing. April 5. Cranium: nothing abnormal. April 8. Extremities, columna, pelvis: nothing abnormal.

DISCUSSION

The peculiar picture of this disease gave rise to various differential-diagnostic conjectures — at first meningitis, and later sinus thrombosis, angioneurotic edema, parotitis, and sepsis and osteomyelitis, which last diagnoses we accepted, supported by the roentgen reports, although we did not feel quite convinced and, at any rate, had to regard the case as atypical.

The solution came via a review in the Journal of the American Medical Association of Sidbury's article on ICH. On going through the articles listed at the end of the present paper, we found that the peculiar picture of our patient's disease was clinically in perfect agreement with the descriptions of ICH. The roentgenograms were re-examined, and it was now possible to demonstrate the changes characteristic of ICH. The revised roentgen report (by H. Eltorm) reads as follows:

Feb. 20, 1954. X-ray examination of the thorax reveals a slight periosteal thickening of the right lower ribs. No changes in the lungs. Cranium: a marked soft-tissue swelling over the posterior part, in the main covering the posterior parietal and part of the occipital region. No osseous changes. Roentgen diagnosis: periostitis costarum dxt. Soft-tissue swelling of the head (Fig. 1 + 2).

March 1. Thorax: the osseous changes are now so conspicuous that the ribs are about twice their normal thickness. The normal contours of the ribs are clearly to be seen through the thickenings, indicating that the changes are still of the nature of periosteal hyperostosis. The changes involve the 7th—10th ribs and are particularly significant in the 8th rib. Cranium: the soft-tissue swelling has all but disappeared. No osseous changes. Roentgen diagnosis: hyperostosis costarum dxt.

March 10. Thorax: status unchanged. Cranium: nothing abnormal.

March 23. Thorax: status unchanged. Cranium: no cranial changes, but the entire mandible shows a double outline with marked swelling of the overlying soft tissue. The periosteal thickenings are slightly varying in width and not more than 3—4 mm thick. Roentgen diagnosis: hyperostosis costarum dxt. et mandibulae (Fig. 3 + 4).

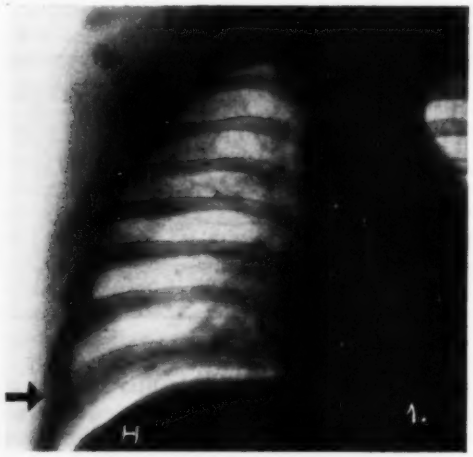


Fig. 1.

Slight periosteal thickening of the ribs. The arrow indicates costa VIII dxt.

Fig. 2.

Soft-tissue swelling over the parietal-occipital region.

April 5. Cranium and mandible: status unchanged.

April 8. Columna, pelvis and extremities: no osseous changes. Thorax: the axillary soft-tissue swelling has diminished. Also the costal changes are receding. The periosteal lamellation is distinct, especially on the under side of the ribs. Roentgen diagnosis: hyperostosis costarum.

May 26. (Follow-up 1 month after discharge). X-ray examination shows continued regression of both the costal and the mandibular changes. The soft tissue surrounding the mandible is, however, still somewhat swollen.

April 19, 1955. (Follow-up 1 year after discharge). Cranium, mandible and extremities: normal conditions. Thorax: a slight thickening of the ribs previously mentioned is observed, but otherwise the structure is normal. Roentgen diagnosis: Hyperostosis costarum, seq. (Fig. 5).

Summary of the case.

A boy aged 4½ months, who had hitherto been in perfect health, and had thrived and developed normally, was taken acutely ill with fever, irritability, soft-tissue swelling of the thorax and head, elevated sedimentation rate, anemia, and

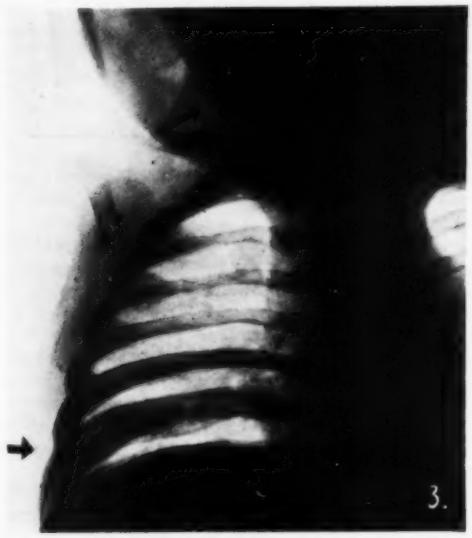


Fig. 3.

Hyperostosis costarum dx. The arrow indicates costa VIII dxt. Double contour lines of the mandible with overlying soft-tissue swelling is also seen.

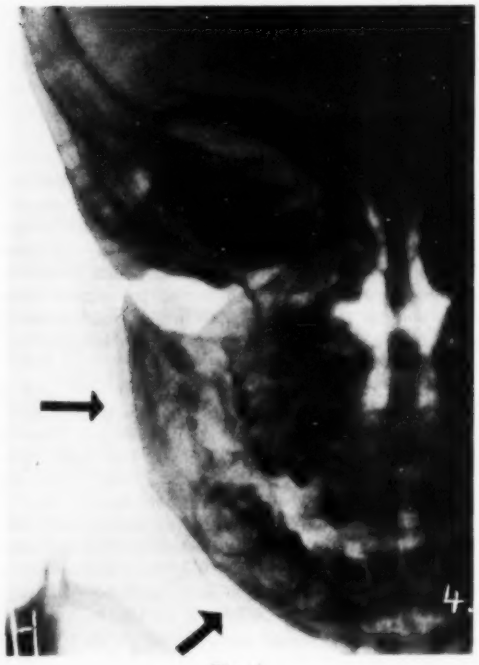


Fig. 4.

Periosteal coatings on the mandible.

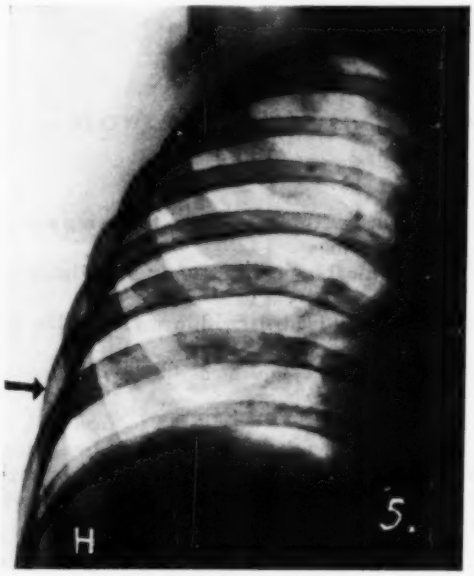


Fig. 5.
Control after one year. Only slight thickening of costae VII—IX.

leucocytosis. The disease was diagnosed sepsis and osteomyelitis. The case was treated with penicillin, Terramycin, Achromycin, and blood transfusions. The disease lasted for about 10 weeks, and its course was characterized by remissions and exacerbations. The patient was discharged in good health. Follow-ups 1 month and 1 year later showed normal conditions.

Later is was realized that the clinical picture of the disorder corresponded exactly to the descriptions published of infantile cortical hyperostosis (Caffey's syndrome). This diagnosis was confirmed by a checking of roentgenograms.

SUMMARY

Infantile cortical hyperostosis is a disorder affecting infants younger than six months of age. The disorder was first described by Caffey in 1945. It is characterized by a sudden tender swelling of soft tissue and cortical hyperostosis in the underlying bones. Hyperirritability, fever, increased sedimentation rate, anemia, and leucocytosis are often associated symptoms.

The duration of the active manifestations varies from a few weeks to several months. The course of the disease is fluctuating with spontaneous remissions and exacerbations. The prognosis is good.

The etiology is unknown. An infectious origin is suspected, but an infective agent has never been found, and the course of the disease has not been modified by the administration of sulfonamides or antibiotics. The pathogenesis is obscure. Pathologico-anatomically, arterial intimal proliferation has been found, and some authors consider this to be the essential of the disease. This arterial intimal proliferation is held to be an inherited defect.

Treatment with ACTH and cortisone seems to shorten the duration of the disease and should be tried in new cases.

A case of the disease in a 4 month-old boy is recorded. This case is the first one reported from Scandinavia.

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ORNITHOSIS

AN ANALYSIS OF 44 HUMAN CASES WITH POSITIVE COMPLEMENT FIXATION TESTS

By MOGENS BORCH JØRGENSEN and KARL ANKER STEFFENSEN

INTRODUCTION

Ornithosis in man has been encountered with increasing frequency during the last few years in Denmark (1, 5, 7, 12, 13) as in several other countries.

There may be a number of reasons for this; two of them are obvious: since 1952 a considerable importation of psittacine birds has taken place; in 1950 The Danish State Serum Institute adopted the ornithosis complement fixation test (11), thus providing an opportunity for the recognition of endemic and sporadic cases.

The purpose of the present report is to analyze the clinical picture of the disease in a fairly large number of cases, and to call attention to the fact that a considerable number of cases with positive complement fixation tests exist which present one or more features deviating from the criteria usually established for the diagnosis of ornithosis in man.

FREQUENCY OF BIRD CONTACT IN HOSPITAL PATIENTS

An attempt was made to gain an impression of the frequency with which a history of contact with birds can be established in the population from which this hospital draws its clientele. From November 1954 through March 1955, 117 patients — a random selection — were questioned, on admission, with regard to contact with birds in the widest sense. 40 of these (34 %) admitted such contact. Of the 117 patients, 40 were children of 15 years or less; 16 of these (37 %) had a positive history of bird contact.

MATERIAL AND CLASSIFICATION

The material comprises all patients with a positive complement fixation test*) for ornithosis seen in this hospital from 1952 to April 1955, a total of 44 patients. As it was found that in 11 of these a previous contact with birds could not be demonstrated, and since in a number of others the magnitude and/or variation of the complement fixation titers raised doubt as to their diagnostic significance, it was decided to divide the entire material into two groups, A and B.

For inclusion in Group A the following criteria were established:

1) the clinical appearance of an acute infectious disease,
2) contact with birds within a reasonable time of the illness,
3) at least one complement fixation test with a titer of 60 or more.

All other cases were referred to Group B.

It is considered that Group A comprises patients with ornithosis in the usual sense. Whether Group B is a homogenous one is uncertain; we shall discuss this later.

The nature of the bird contacts is given in Table 1.

Table 1.
Nature of Bird Contacts.

Parakeets	12 cases
Visit to bird shops	10 »
Canaries	4 »
Parrots	3 »
Pigeons	3 »
Blackbirds	1 »

Sex and age distribution: Group A comprises 27 patients, 14 males and 13 females; Group B 17 patients, 10 males and 7 females.

The age-distribution is given in Fig. 1. Group A ranges from 20 to 70 years, with maximum in the fourth decade. In Group B the range is from

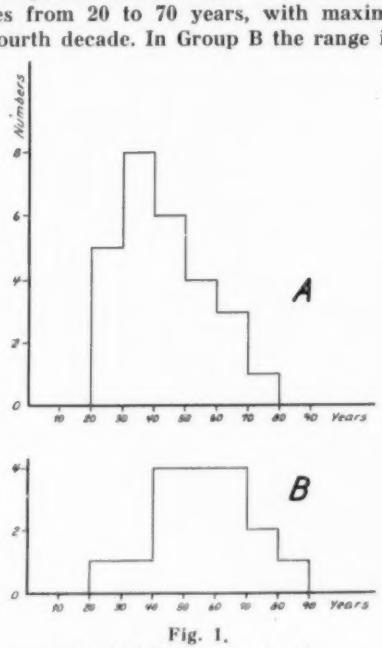

Fig. 1.
Age distribution by decades.

From: Blegdamshospitalet, Epidemihospitalet, Copenhagen. Head: Prof. *H. C. A. Lassen.*

*) We are indebted to Dr. *M. Volkert* and Dr. *P. Møller Christensen* of the State Serum Institute, and their department, for making the tests and for helpful discussion.

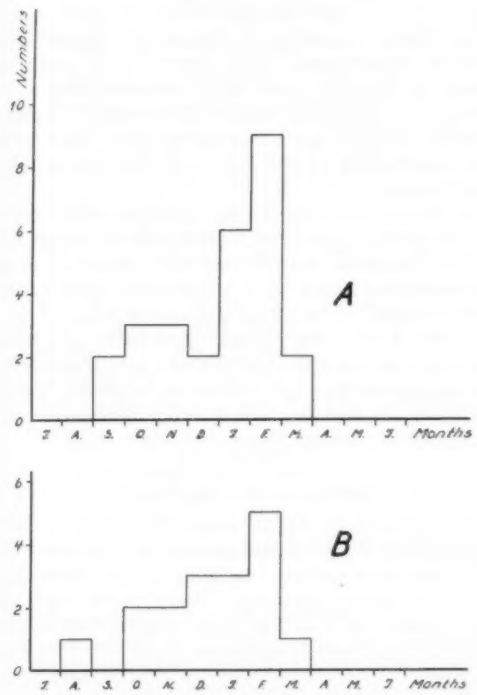

Fig. 2.
Distribution of cases according to the month in which the illness began.

25 to 80 years, with maximum in the fifth to seventh decades. It will be noted that children are absent from either group.

The distinct seasonal variation is seen from Fig. 2. — The first of our patients fell ill in February 1953. Both groups show maximum incidence in the month of February, and no cases were encountered in the period April through July. (After the completion of this study, however, we have seen 9 cases, of which 8 started later than April 1., viz. 1 in April, 3 in May, 2 in June, and 2 in July 55. Five of these cases would have fallen in Group A).

The distribution of the cases over the three seasons covered by this study is illustrated in Table 2. The remarkable increase in the number of cases is readily seen and is somewhat more pronounced in Group B.

Table 2.
Distribution of Cases over 3 Years.

	Group A	Group B	Total
1952—53	1	0	1
1953—54	8	1	9
1954—55	18	16	34
	27	17	44

INCUBATION PERIOD

An estimate of the incubation period could be made only in a few cases; in some of these it appeared remarkably long. Thus, a woman of 47 had fed the pigeons on the Piazza San Marco in Venice, and was taken ill 1½ months later; she would admit to absolutely no other avian contact. A woman of 70, who fell ill on November 3rd, had been petting some young blackbirds in her garden, sometime during September, an incubation period of 1½ months or more. — On the other hand, cases were seen with incubation periods of about one week.

CLINICAL COURSE

The disease has a sudden onset, with chills and a rise of temperature to 39—40° C. in one or two days. High fever persists for about one week, after which the fall is lytic; very often the temperature curve tails out in a prolonged subfebrile course. Secondary bouts of fever and true relapses are frequent and constitute a characteristic feature of ornithosis. — During the initial stage patients complain of headache, and aches and pains of varying localization. A slightly sore throat and nasal congestion are often present. — After a few days a dry, non-productive cough sets in; dyspnea is usually absent. Photophobia, conjunctivitis and epistaxis, so often mentioned in previous descriptions, were not prominent in this series. A few patients had diarrhoea as an early symptom, but most were mildly constipated. In several instances localized symptoms were entirely absent, the picture being that of a quite uncharacteristic continuous fever.

On physical examination the majority of patients do not appear very ill. The pulse rate is relatively slow. At some time stethoscopy of the lungs usually reveals diminished breath sounds and râles. — A definitely enlarged spleen was practically never demonstrated.

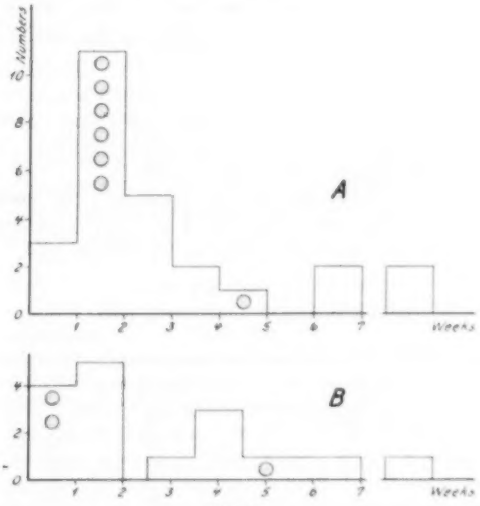

Fig. 3.
Distribution of cases according to duration of fever. Each circle indicates a relapse.

None of our patients died of ornithosis, and the classical, very severe picture, known from earlier accounts of psittacosis, was hardly ever encountered.

The variation in the duration of fever in the present series is illustrated in Fig. 3. — Three patients were febrile for more than 7 weeks; one for a total of 82 days; the remaining two had complicating diseases for which they were transferred to other hospitals. In both groups there is a tendency towards a more protracted course in the elderly patient, illustrated by the fact that all patients with fever of more than 4 weeks' duration were 50 years old or more.

A true relapse exists when, after a completely afebrile interval, fever recurs. Rather often, however, a definite drop in temperature to subfebrile levels is followed, after some time, by a secondary bout of fever. The number of patients with relapses of either type was 13 in Group A (48 %), and 12 in Group B (70 %).

Typical relative bradycardia, with a pulse rate of about 80 per minute, when the temperature is 39—40° C., was seen in 1/3 of the patients in the entire series; in 1/3 this phenomenon was less prominent, and in 1/3 absent.

The sedimentation rate is usually markedly elevated, though wide variations occur, as will be seen from Table 3. Often the rate is seen to increase through the first two weeks of illness, and it may persist at high levels for a considerable time.

Table 3.
Sedimentation Rate.
(mm per hour)

	Group A		Group B	
	Mean	Range	Mean	Range
1st week	72	15—115	86	25—138
2nd week	61	20—133	60	33—75
3rd week	48	17—101	50	4—106

Leucocyte counts were made in 17 patients of Group A. 14 had from 4,000 to 10,000 leucocytes per mm^3; 3 had counts between 10,000 and 12,000. Differential counts were essentially normal. In Group B results were quite similar.

Table 4 summarizes the frequency of some clinical symptoms in Groups A and B. No striking differences are seen between the two groups.

Table 4.
Frequency of Some Symptoms
(per cent)

	Group A	Group B
Temp above 39°C.	89	94
Chills	67	41
Pain	67	59
Headache	78	35
Cough	81	76
Expectoration	26	47
Sore Throat	22	18
Vomiting	22	18

X-RAY FINDINGS

On X-ray examination, signs of recent pulmonary involvement were found in 22 cases in Group A (82 %). All of these showed patchy infiltrations consistent with pneumonitis, whereas pleural changes were not noted. The right lung was affected in 15, the left in 4. Three had bilateral lesions.

In Group B roentgenologic changes were found in 15 (88 %); two of these had pleural densities; in the remainder the findings were interpreted as pneumonitis. There were 7 right-sided and 7 left-sided lesions; 1 had bilateral changes.

Chest X-ray was done repeatedly in most patients; as a rule the changes are seen quite early in the course. In a few instances, however, roentgenologic lesions did not develop until after the 14th day of illness.

SEROLOGICAL FEATURES

The graphs in Fig. 4 depict the titers of the complement fixation tests and their variations in the individual patient. In both groups there are cases in which significant titers occur early in the disease (3rd to 5th day), whereas in others negative tests are found even up to the 20th day of illness, whereafter a rise in titer occurs.

It will be noted that in Group A the tendency is towards a rise in titer during the period of observation, some cases reaching maximum in about 20 days, while in others the increase extends over periods up to 3 months.

In Group B, on the other hand, the trend is towards a fall in titer over the first 20 days of the disease.

COMPLICATIONS

Thrombophlebitis of the lower extremities was seen in 2 patients of Group A, and 3 of Group B.

Pyuria was seen in 2 patients of Group A and 3 of Group B.

Microscopic haematuria was encountered once in Group A and in 3 patients of Group B.

Transitory proteinuria was seen in 11 patients of Group A, and in 7 of Group B.

A woman of 23 (Group A) was 9 months pregnant. She had a mild course with fever of only 6 days' duration, and shortly afterwards gave birth to a healthy child.

Pulmonary tuberculosis, not diagnosed before, was found in a man of 30 (Group A) and a woman of 35 (Group B). In both m. tuberculosis was demonstrated from sputum and gastric lavage.

A man, 57 years old, had cancer of the right lung. He was transferred to a department of thoracic surgery and died 11 days after the removal of an anaplastic carcinoma.

TREATMENT

Treatment in this series included sulfonamides, penicillin, chlortetracycline, and oxytetracycline.

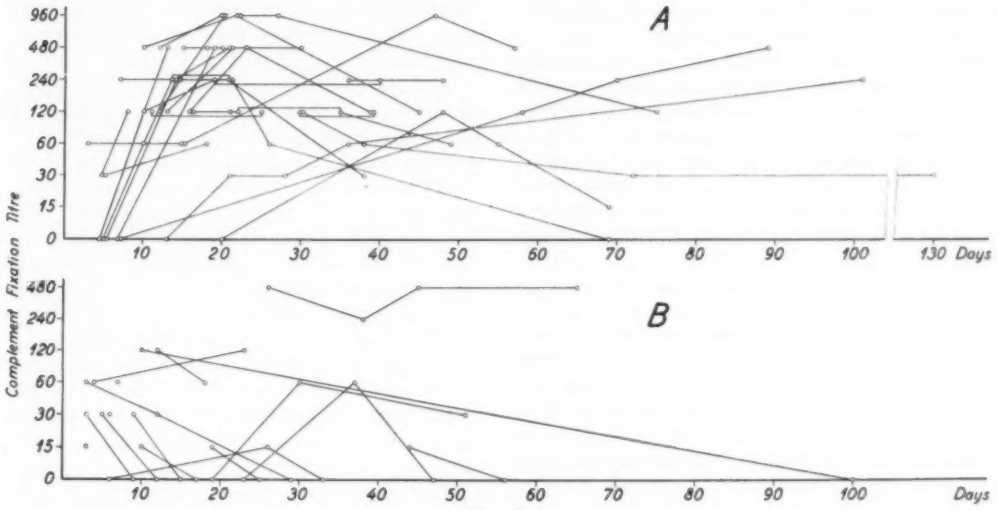

Fig. 4.
Course of the Complement Fixation Titers in the Individual Patients.

The sulfonamides are probably of no value in the treatment of ornithosis. — In experimental infections (chick-embryos, mice) penicillin and the tetracyclines have shown activity against the virus of ornithosis; the tetracyclines are superior to penicillin in this respect. The virus is, however, readily recovered from infected tissues after treatment. — Clinical experience agrees well with experimental findings; there are numerous reports on the favourable effect of these antibiotics on the course of ornithosis in man (summarized in 2). This is most striking in laboratory infections, where the infecting agent and the time of infection are known, and treatment can be initiated at an early time. Meyer and Eddie (8) have reported good response to penicillin in three such cases. Volkert and Møller Christensen observed prompt effect of Aureomycin in laboratory infections. Unfortunately, most clinical studies are uncontrolled and suffer from the limitations imposed by delay in diagnosis and treatment; this is also true in the present series. The following is a brief presentation of therapeutic data in Group A.

6 patients were left utreated. The duration of fever was from 7 to 20 days, average 11.4 days.

5 patients had penicillin-procaine, 300,000 u. daily for 6 days. The duration of fever was from 5 to 14 days, average 10.6 days.

3 patients had Aureomycin in a daily, divided dose of 1 g for 6, 6 and 10 days. Treatment was begun on the 15th, 12th and 17th day, respectively. The duration of fever was 17, 12 and 30 days.

3 patients first had penicillin for from 1 to 7 days, then Aureomycin (dosage as above) for 6 days. Total duration of fever was 11, 12 and 15 days, respectively.

One patient had oxytetracycline, 750 mg daily for 12 days. Treatment was started late in the course (on the 21st day); after 48 hours the temperature fell to a subfebrile level, where it persisted for several weeks.

Of the remaining 9 patients of Group A, some had various combinations of sulfonamides and penicillin, some had penicillin by mouth. In a few, for various reasons, the therapeutic regimen was quite obviously insufficient. — In this group of 9 patients the duration of fever varied from 10 to 45 days, average 21.5 days.

Most of the patients in this series have been seen in the hospital by the authors. It is our impression that both penicillin and Aureomycin exert a favourable influence upon the course of ornithosis in man; but the effect is not always very striking.

DISCUSSION

It is the impression from this study that ornithosis is becoming a rather common disease in Copenhagen. It is seen with increasing frequency, a fact which is hardly explained entirely by improved diagnostic possibilities.

The clinical picture of the disease is mainly that known from early descriptions, with the exception that the course is milder and lethality negligible.

As the demonstration of virus from the patients was not practicable, the chief diagnostic criterion was a positive complement fixation test. The limitations of this test are well known, but in our opinion not very significant; it is positive in certain related diseases, which have never been met with in this country, and in lymphogranuloma venereum, which is very rare. Certain inhibiting factors in serum may cause false negative

reactions, particularly in avian blood, but presumably in some human sera also.

When our groups A and B are compared, they are nearly identical as regards seasonal distribution, age of the patients, clinical picture and course, roentgenological signs, and frequency of relapses. The resemblance is so great that a distinction between the two groups might seem quite artificial. The differences in serological findings are, at least in part, due to the definition of the groups.

We believe, therefore, that a positive complement fixation test is practically always an indication of the presence of ornithosis or some closely related disease. The question whether such related diseases actually occur in this country can only be solved by isolation of the causative virus. Such studies will also be necessary for the detection of the source of infection in patients who have had no contact with birds.

Spread from human sources seems to occur very rarely. A few cases have been described in literature (4, 5, 6, 10); most often nursing personnel or neighbouring patients were infected from severely ill persons. On the other hand, a clinically healthy individual is known to have harboured ornithosis virus for 8 years, without giving rise to new infections (9).

In our series no instance was found in which previous contact with another human case of ornithosis could be ascertained. Elkeles and Barros (3) point out that the indirect transmission of virus is a possibility that should be suspected in cases without contact with birds; this may be the explanation in some of our cases too.

SUMMARY

An analysis is given of 44 patients with positive ornithosis complement fixation tests, seen in the Blegdamshospital, Copenhagen, during 1952 to April 1955. A marked increase in the number of cases during this period was noted.

In some cases no contact with birds could be demonstrated; others had low complement fixation titers. A comparison was made between such dubious cases (Group B) and the cases in which the diagnosis of ornithosis was considered certain (Group A). Epidemiological and clinical features were not significantly different in the two groups, and it is concluded that practically all the patients suffered from ornithosis or some closely related disease, indistinguishable from ornithosis in the absence of virus studies.

The clinical picture is much the same as that known from previous descriptions, but the course is generally milder and there were no deaths.

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RESULTS OF LONG-TERM TREATMENT OF RHEUMATOID ARTHRITIS

AN ATTEMPT AT A COMPARATIVE EVALUATION OF CORTISONE AND CORTICOTROPHIN THERAPY

By R. JORDAL

During the past five years the problems connected with long-term treatment of rheumatoid arthritis with cortisone have been richly elucidated in numerous works. Considerably fewer experiences are available as regards continuous treatment with Corticotrophin, as such therapy has been carried through in a very limited number of cases. This is no doubt due to the lack of suitable preparations and to a reluctance to give treatment by injections in cases where an effective peroral treatment may be offered to the patients.

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Previous Studies.

Holbrook & al. (12) in 1951 presented a material of 35 rheumatoid arthritis patients who had been treated with Corticotrophin for periods ranging from 6 to 19 months. The results at the end of the treatment were as follows:

20 per cent showed complete clinical remission (grade 1).

40 per cent showed satisfactory clinical remission — grades 2 and 3 (with development of slight hypercortisonism).

40 per cent showed an unsatisfactory result (grades 3 and 4) owing to toxic manifestations with rapidly developed resistance to Corticotrophin; however, large doses still of effect.

Holbrook (8) in 1955 published the results of Corticotrophin therapy continued for periods of up to fours years. This material also consisted of 35 patients, for whom prolonged treatment had been considered suitable. The principle of treatment was to aim at as complete a suppression of symptoms as possible by means of doses of up to 60 units per day. The results were as follows (the figures in parentheses indicate the number of patients under treatment at the time in question, seeing that patients who developed toxic symptoms, or showed serious progression despite treatment, were taken off therapy):

Improved after	2 weeks'	treatment		(35)	34	grade	1 or 2
"	" 6 months'	"		(23)	19	"	"
"	" 12	"	"	(12)	9	"	"
"	" 24	"	"	(7)	1	"	"
"	" 36	"	"	(2)	0	"	"
"	" 48	"	"	(1)	0	"	"

By way of comparison, Holbrook mentions that he obtained considerably better results during an observation period of the same length in a material of patients receiving a much smaller dose (10 units 3 times a week). No detailed account is given, but the result is stated to be equal to that obtained with a subsequent material where cortisone in small doses (50 mg or less per day) was administered to the patients:

Improved after	12	months'	treatment		50	out of	60
"	" 24	"	"		41	" "	60
"	" 36	"	"		29	" "	60
"	" 48	"	"		26	" "	60

The author makes no further comparison between the results of Corticotrophin and cortisone therapy.

Brugsch & Gowans (3) treated 100 elderly rheumatoid arthritis patients with Corticotrophin in doses of 60—80 units daily, and report that, with a few exceptions, they all showed striking subjective improvement and a marked increase in physical ability. Measured by the commonly adopted objective criteria (Steinbrocher & al., 15), the improvements were less pronounced. No details are given of the composition of the material or the length of the period of treatment. Finally, the authors compare the outcome of cortisone treatment with that of Corticotrophin therapy and find that Corticotrophin in the said dosage gives the same result as 75—100 mg of cortisone per day; however, they find that Corticotrophin produces a more rapid and pronounced effect and, furthermore, gives favourable results in cases in which cortisone seems to have brought about a state of refractoriness. Besides, they find that Corticotrophin has a better effect on severely disabled patients. As the most serious secondary effects, edema and diabetes are mentioned; local side effects occurred in a few cases in the form of painful infiltrations at the sites of injection.

West & Newns (16) subjected 11 patients to continuous therapy with Corticotrophin for periods of 12—24 months. They tried to solve the difficult question of dosage (see later) by regularly determining the daily excretion of 17-ketosteroids, which they endeavoured to keep between 15 and 40 mg according to the clinical effect. As a rule, this end was achieved by means of a daily dose of Corticotrophin ranging between 7.5 and 40 units. The results are stated as average values of the physical ability of the patients, numerically rated in accordance with the criteria of the Medical Research Council & Nuffield Foundation, and the average values, before and during treatment, of

	Before treatment	During treatment
SR	38	19 mm /hour
Grasping strength of right hand	88	174 mm Hg
Grasping strength of left hand	79	171 mm Hg
Hb.	12.3	13.3 g /100 ml
Leucocytes	9600	10900 per cmm
Weight	59	65 kg.
Blood pressure	127/77	135/84 mm Hg
Physical ability	3.2	2.1

Finally, after making a comparison with a similar material treated with cortisone, the authors concluded that the results, evaluated by the above criteria, were most favourable in the case of Corticotrophin therapy. Also in the progression of bone destruction during the treatment a marked difference was noted, progression being observed in 59 per cent of the patients in the cortisone material as compared with only 18 per cent of the Corticotrophin patients. As regards secondary effects, it is mentioned that the Corticotrophin group showed the greatest increase in weight. No cases of anaphylactic reactions or development of resistance were observed.

Goslings & al. (5, 6) combined Corticotrophin treatment with chrysotherapy. For periods of 6 weeks—8 months, 20 patients were given Corticotrophin, supplemented after a suitable time with gold preparations. Result: none of the patients obtained a remission that was maintained after the treatment. At one time or other during the period of treatment, 17 of the

patients experienced complete or major improvement, while 3 showed only minor improvement. At the cessation of therapy only 8 patients were satisfactorily improved, while 4 showed little improvement, and in 8 patients progression of the disease was observed. Ordinary Corticotrophin was used, and the greatest difficulty connected with the treatment was that several of the patients soon developed resistance to the preparations (see later).

MATERIAL

At the Medical Department of the Frederiksborg County Central Hospital we have consistently used Corticotrophin in our attempts at protracted therapy in rheumatoid arthritis for reasons that will be discussed later.

The material consists of 48 patients, distributed as follows:

45 suffering from rheumatoid arthritis: 13 men and 32 women.

3 suffering from rheumatoid spondylitis: 2 men and 1 woman.

The distribution of the 45 patients according to the stage of disease is:

Stage 1: 2
Stage 2: 20
Stage 3: 17
Stage 4: 6

Indications.

Although we were fairly broad-minded in our indications for Corticotrophin therapy, we always insisted on the disease being in an active phase (judging by SR, temperature and objective articular changes). Less importance was attached to the duration and stage of the disease and the therapy given previously. As absolute contraindications we counted only incompensated cardiac disease, active tuberculosis, symptomatic gastroduodenitis, and pregnancy, but not diabetes mellitus.

Principles of Treatment.

In all cases the hospital treatment was started after a certain period of observation, because the hospitalization in itself may cause a lessening of the symptoms of the patient. During this period the patient was subjected to a careful examination as to physical ability, working capacity, joint status, etc. As a matter of principle, only one preparation was used, as we share the view of Goslings & al. (7) that the different preparations and even batches are so dissimilar in standardization that a change from one preparation to another will very soon lead to uneven reaction (2). We used Acton prolongatum and, on the whole, observed few undesirable effects of this drug.

The first patients treated were given an initial dose of 20 units per day for 3—4 days, after which the dosage was gradually reduced to a level at which the patient felt a moderate effect. Rather soon we learned, however, that better results were obtained in the long run if both the initial dose and the maintenance dose were reduced. The reason for using a larger initial dose is that it seems to stimulate the adrenal glands so as to make them respond more favourably to the small maintenance doses (13). We endeavoured to keep the intervals between the individual injections within a maximum length of 36 hours, as it is doubtful whether even the best long-acting preparations maintain their effect beyond that period. During the subsequent ambulant control, doses were always adjusted according to the stress at the moment.

Additional therapy consisted in active and passive movements, administration of magnyl as analgetic in as small doses as possible and, frequently, intra-articular injections of hydrocortisone in the two or three most pain-affected joints. The patients were taken out of bed as soon the temperature had become normal.

In view of secondary effects, the patients were at first given rigid prescriptions directing a diet low in salt (< 1 g NaCl per day) and an additional supply of potassium; however, we later realized that such inconvenient impositions were unnecessary, and we now confine ourselves to recommending the patients to avoid eating salt dishes and taking salt with their food, and have ceased prescribing an additional supply of potassium.

Control of Treatment.

During their stay in hospital we followed the patients' weight, blood pressure, SR, leucocyte count, tendency to edema, and protein and sugar content of the urine. On the other hand, we considered it unnecessary to make a routine duty of following the electrolyte content of the blood. At the ambulant control, taking place at intervals of some weeks to begin with, later at intervals of some months, according to the state of the patients, we made the same examinations. Every three months the lungs of the patients were x-rayed. After 6 and 12 months of continuous therapy, a more thorough examination was made to establish the effect of the treatment, particular attention being paid to the physical ability of the patients and their consumption of analgetics.

RESULTS

For the evaluation of the results we have employed Steinbrochers's criteria (15), although we are perfectly aware that they can give no true picture, since many patients experienced an improvement that found no numerical expression (which is probably due to the fact that these methods attach most importance to mobility changes; considering the generalized nature of rheumatoid arthritis, this is no doubt a mistake). The therapeutic results as seen in relation to the

Table 1.

Summing-up of results according to: 1. Stage of disease:	Number of patients	1°		2°		3° + 4°		Treatment ceased: Favourable result		Unfavourable result	
		½ year	1 year	½ year	1 year	½ year	1 year	½ year	1 year	½ year	1 year
Stage 1:	2	1	0	0	1	0	0	0	0	1	1
Stage 2:	20	6	4	9	8	3	1	0	1	2	6
Stage 3:	17	0	0	12	5	2	2	1	3	2	7
Stage 4:	6	0	0	4	3	2	1	0	0	0	2
Spondylitis:	3	1	1	1	1	0	0	0	0	1	1
2. Duration of disease:											
0— 4 years	22	6	3	8	7	3	1	1	3	4	8
5— 9 years	7	0	0	6	3	1	0	0	0	0	2
10—14 years	10	1	1	7	5	1	3	0	1	1	2
>15 years	9	1	1	5	3	2	0	0	0	1	5
3. Age of patients:											
20—29 years	2	1	0	0	0	0	0	0	1	1	1
30—39 years	4	1	1	3	2	0	0	0	0	0	1
40—49 years	12	3	2	6	5	2	1	0	0	1	4
50—59 years	13	2	1	6	4	2	1	1	1	2	6
60—69 years	15	1	1	9	6	3	1	0	2	2	5
>70 years	2	0	0	2	4	0	1	0	0	0	0
4. Sex of patients:											
Men	15	1	0	9	5	0	1	0	1	5	8
Women	33	7	5	17	13	7	3	1	3	1	9
Total number of patients:	48	8	5	26	18	7	4	1	4	6	17

stage and duration of the disease and the age and sex of the patients are shown in Table 1. It is difficult to indicate exact values for the maintenance dose, seeing that the dosage was frequently changed and that the daily dose was dependent on both the size of the individual injections and the interval between them. For the summing-up of results, we have used the dosage in the period immediately prior to the bi-annual evaluations. The results in relation to dosage are seen in Figures 1 and 2.

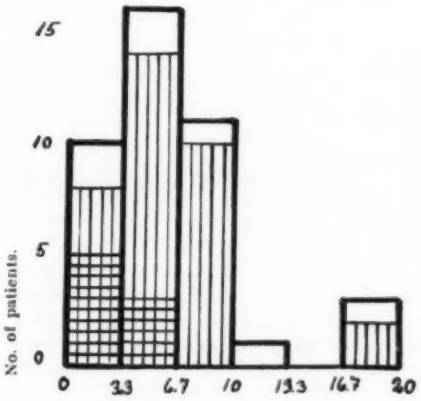

Fig. 1.

Results after 6 months' treatment shown in relation to size af daily dose. The ordinate indicates the absolute number of patients, the abscissa the size of the daily dose.

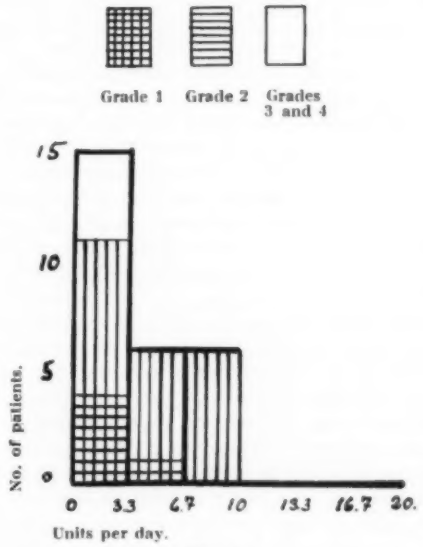

Fig. 2.

Results after 12 months' treatment shown in relation to size of daily dose. The ordinate indicates the absolute number of patients, the abscissa the size of the daily dose in int. units.

Secondary Effects.

These shall only be mentioned briefly as they are not essentially different from those observed in connection with cortisone therapy. The nature and frequency of the side effects appear from Table 2, but a few comments should be made on one or two of them. There seemed to be indica-

tions that the liquid-retaining effect of Corticotrophin was greater than that of cortisone; however, only in one case did this circumstance necessitate discontinuance of the treatment, while in all other cases it was possible to control it through a reduction of the salt intake. In many instances the liquid retention was a transitory phenomenon.

Table 2.

Moon face	23
Weight increase	19
Edema	17
Increase in blood pressure	5
Hypercortisonistic pseudorheumatism	5
Menstrual disturbances	5
Transitory mania	5
Glossitis, stomatitis	4
Infiltrations at sites of injection	4
Glucosuria	3
Cardiac insufficiency	3
Headache	3
Transitory depressions	3
Acne	2
Loss of hair	2
Hypertrichosis	1
Gastroduodenitis	1
Retarded healing of wounds	1
Heat flashes	1
Diabetes mellitus	1
Ecchymoses	1
Fracture (adequate trauma)	1

Four patients developed some symptoms of mucose membrane affections (stomatitis and glossitis), different from those previously reported. The symptoms appeared after about one month's therapy (and flared up immediately after every injection). The explanation is no doubt that the patients in question developed hypersensitiveness to the preparation or to impurities contained therein. The same is probably true of the tender infiltrations found at the sites of injection in 4 patients; they occurred most frequently within a well-defined period and were presumably accounted for by one particular series of the preparation. An attempt to prevent these reactions with antihistaminics turned out to be negative. The glucosuria was temporary in all three cases, and no investigation was made into its cause. The diabetes mellitus case was a patient in whose family there were several sufferers from this disease.

In our instructions to the patients we made a point of calling their attention to the complications that may result from the treatment: the risk of injection, and adrenal shock at discontinuation of therapy or in connection with large traumas or operations. We observed no case of infection after the Corticotrophin injections and the numerous intra-articular injections of hydrocortisone. (Later we have, however, found one case of purulent arthritis following such an injection; to all apperances it was due to an infected local anesthetic). Nor did we observe any case of adrenal shock, not even in the patients who — contrary to our instructions — discontinued treatment without any preceding tapering of the dose.

Development of resistance, as known from several works (5, 6, 12) was found in 12 patients. The phenomenon occurred after 2—10 months of treatment and in 5 cases was so pronounced that therapy had to be discontinued since, to obtain a satisfactory effect, doses had to be increased so much as to reach a level not devoid of risk. In one patient we changed to cortisone, which proved to be of good effect in a dose equal to the Corticotrophine dose previously administered. In 6 patients it was possible to obtain a satisfactory effect by a reasonable increase in dosage.

The reasons why 21 patients failed to carry through the treatment for the entire period of investigation, are a point of special interest:

4 stopped treatment because sustained remission occurred. 6 stopped treatment on account of serious side effects:

2 severe cases of hypercortisonistic pseudorheumatism, one of which has been described by T. Andersen (1). 2 developed psychotic conditions. 1 developed diabetes mellitus. 1 had severe edema.

In 11 patients the effect ceased after treatment periods af varying length, for which reason therapy was discontinued at their own request. A comparison of the number of patients withdrawn from therapy in the course of the second six months with the daily doses administered to them at the beginning of that period leads to the interesting result, in agreement with Holbrook's experiences (8), that the greatest number of patients taken off treatment were found among those receiving the largest doses (Fig. 3).

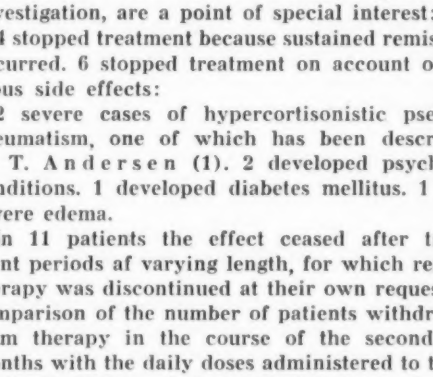

Fig. 3.

The abscissa indicates the size of the daily dose at the end of 6 months' treatment. The ordinate indicates, in percentage of the number of patients treated, the number of patients who had to discontinue treatment during the second 6 months owing to secondary effects or absence of effect.

DISCUSSION AND CONCLUSION

The present investigations were designed 1) to examine whether it is practically possible to carry through a long-term treatment with Corticotrophin; 2) to examine whether the effects of

such a treatment are essentially different from those of cortisone therapy; 3) to contribute to the experiences with protracted treatment of rheumatoid arthritis with adrenal cortical steroids as the active principle.

Re 1. The material here presented provides an answer in the affirmative, and the greater purity of future preparations will probably bring about an improvement of the results.

Re 2. It is common to Corticotrophin and cortisone treatment that the aim is to increase the content of cortisone-like substances in the blood in order to delay the tissue reaction that is the cause of some of the symptoms of the patients. Accordingly, the results and secondary effects of the two therapeutic methods are, on the whole, alike. The difference between the two kinds of treatment is that not only is atrophy of the adrenal cortex avoided in the case of Corticotrophin administration, but there is even adrenal hypertrophy. This must be considered an advantage, both at the cessation of therapy and in the case of increased stress during the treatment involving the risk of deficiency of adrenal cortical hormones in the organism. Through investigations into the hormonal changes in the blood following withdrawl of Corticotrophin, it has been demonstrated (11) that first there is a short phase of hypocortisonemia, which is succeded by a hypercortisonemic phase; the reason for this change is most likely that the hypocortisonemia causes the pituitary to increase its secretion of Corticotrophin beyond what is necessary to maintain the "status quo", and in the Corticotrophin-treated organism the adrenal glands are capable of reacting at once to secretional stimuli. Afterwards (possibly after several alternating hypo-hypercortisonemic phases) the secretion becomes normal. If this is so, it explains why the abstinence symptoms and signs of relative insufficiency of the adrenal cortex frequently met with after withdrawal of cortisone are never observed after the cessation of Corticotrophin treatment.

After dealing above with certain advantages connected with the Corticotrophin treatment, we shall now turn our attention to the objections that may be made against it:

a. The risk of adrenal haemorrhages. With the dosage used this risk must be small. In the cases where this calamity has been found to develop, a considerably higher dosage was used. Besides, the said complication has also been observed to develop in patients under cortisone treatment (19).

b. The adrenal glands of different patients respond differently to the same dose of Corticotrophin. For this reason the dosage must be adapted to individual needs, but then this applies to cortisone treatment as well, and whether the individualization according to therapeutic effect is made in units or mg is a matter of secondary importance.

c. The effect is dependent on unimpaired function of the adrenal cortex. In certain patients in whom Corticotrophin produces an unsatisfactory effect, the reason may be inadequate function of the adrenal cortex. However, we subjected patients of this type to an examination of the adrenocortical functions and found these to be normal. In agreement herewith the same patients have not experienced any effect of cortisone treatment later on.

d. The potency of the preparations vary from factory to factory and from series to series (2, 7). This is probably the most serious objection that can be made, but practical experiences prove that this difficulty may be surmounted through consistent use of the same preparation.

e. Corticotrophin is to be administered by injection, which is no doubt a drawback; however, our patients have never complained.

f. A refractory stage often occurs during Corticotrophin therapy. To all appearances the explanation is that the rapidity with which the injected Corticotrophin is decomposed by the organism, gradually increases; especially this applies to impure preparations (10). Another explanation is that the development of resistance is only apparent, as the phenomenon developed may in reality be the symptom complex described by Slocumb (14): hypercortisonistic pseudorheumatism.

It is thus our view at present that Corticotrophin should be preferred for long-term treatment of diseases (e. g. rheumatoid arthritis) in which the adrenal cortex functions normally according to our present knowledge, while cortisone is to be preferred where the adrenal cortex is already under maximum stimulation (e. g. fulminant infections such as the Waterhouse-Friederichsen syndrome) and a further supply of adrenal cortical hormones is wanted.

Re 3. With our present knowledge we are of the opinion that it is extremely important to use the smallest possible dose in long-term treatment of rheumatoid arthritis with adrenal cortex as the active principle, which means that Corticotrophin and cortisone should only be an aid to the rehabilitation of the patient. This view is strengthened when the following fact is borne in mind: through X-ray control of patients treated with cortisone it has been demonstrated (4) that the articular bone destruction is in constant progression even if the therapy produces a good effect, which means that even intensive hormone treatment can, at best, only retard the development of the disease. Further, the chance of failure of the protracted treatment is greatest when large doses are applied. Therefore, the temptation to obtain the immediate brilliant effect produced by large doses should be resisted.

SUMMARY

45 patients with rheumatoid arthritis and 3 patients with rheumatoid spondylitis were given

long-term therapy with Corticotrophin, and the result was summed up after treatment periods of six and twelve months. After six months a satisfactory result was observed in 73 per cent of the patients, after twelve months in 56 per cent. The secondary effects of the treatment were of the same nature and magnitude as those produced by cortisone therapy.

A comparison is made between cortisone and Corticothropin therapy, and it is given as our opinion that the latter drug should be preferred for long-term therapy, above all because atrophy of the adrenal cortex is thereby avoided, while cortisone should be used in acute situations where the adrenal glands are already under maximum stimulation. Finally it is emphasized that the dose applied should be as small as possible.

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TWO CASES OF SCHISTOSOMIASIS (BILHARZIASIS) IN DENMARK

By POVL RIIS

The rapidly increasing possibilities of travel in the past years have augmented the rate of isolated cases of endemic diseases met with in parts of the world far from the corresponding endemic areas.

This means that endemic diseases have to be included in differential diagnosing in non-endemic areas on a larger scale than before.

These facts justify the following report of two cases of *schistosomiasis haematobium (bilharziasis)* in two Danish siblings.

Case 1. (J. No. H 1581/55). 12 year old girl, previously healthy. 3 months before admission returned from Swaziland, South Africa, where bilharziasis is endemic. The day of admission acutely ill with severe pains in the right side of the abdomen. No symptoms from the lower urinary tract. Temperature normal. Examinations: The urine was bright yellow with small particles of coagulated blood. It gave a positive benzidine reaction and a positive Heller's test. Several leukocytes and erythrocytes were seen by microscopy. Cystoscopy revealed a slight congestion, edema and small yellow granulations around the ureteric orifices. The same lesions were found in a small area superior to the base of the bladder. It was not possible to take a biopsy specimen. These lesions were at first suspected to be tuberculous, but TB could not be demonstrated. E. S. R. 16 and 10 mm per hour. Haemoglobin 80 per cent. Tymol test 0.23 and 0.32. Eosinophils 344/mm^3. X-ray examinations of the urinary tract and lungs were normal. All other examinations showed nothing abnormal. Ova of schistosoma haematobium were finally detected in the urine. (see: Diagnosis).

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Case 2. (J. No. F 1772/55). 9 year old boy, a brother of Case 1. Previously healthy. Seven months before admission returned from Swaziland. During these months pronounced haematuria with dysuria and pains in the lumbar regions, as well as tiredness. No fever periods.

Examinations: E. S. R. 15—20 mm/h. Haemoglobin 85 per cent. Urine microscopy: several leukocytes and erythrocytes. Heller's test positive. Serum urea 31 mg per cent. Creatinine-clearance 29 and 40 ml. X-ray examination of the urinary tract showed no concrements but a delayed excretion on the left side besides a strongly dilated left pelvis and right ureter (Fig. 1). Cystoscopy was avoided, the diagnosis being confirmed by the detection of ova. Fibrinogen 0.41 per cent. All other examinations showed nothing abnormal.

Ova of schistosoma haematobium were found in large quantities.

Etiology and Pathogenesis.

Schistosoma haematobium, or *bilharzia haematobia*, belongs to the blood flukes. Its geographical distribution is confined mostly to Africa, but it is also known in Portugal, Spain, Greece and the Levant (1). It is the Egyptian disease *par excellence*.

Fig. 1.
Intravenous urography in Case 2 sixty minutes p. c.

The adult parasite inhabits the veins, especially the veins of the urinary tract. The eggs pass into the urine and hatch in fresh water to *miracidia*. These invade an intermediate snail host and give rise to *sporocysts*. *Cercariae* then appear in the sporocyst and leave the snail through the pulmonary cavity. The cercaria penetrate the mucous membranes of the pharynx or — more often — the skin of the human host, when he drinks or comes into cutaneous contact with polluted water. The young flukes are then carried to the characteristic locations in the portal system and so the cycle is completed.

Pathology and Symptomatology.

Schistosoma haematobium constantly affects the urogenital tract as well as, to a varying degree, the liver, spleen, lungs and the central nervous system.

A variety of genito-urinary lesions are the consequence of bilharzia infection and its sequelae. The kidneys may be the site of pyelonephritis and hydronephrosis or pelvic papillomas, the ureters of hydroureter, calculi and tortuosity or kinking. The bladder is often primarily involved and may show almost every form of lesions: granular and papillary cystitis, cystic lesions, ulcerative cystitis with the formation of necrosis, intramural fibrosis and contraction, calculus formation, papillomas, carcinomas and vesical fistulas and sinuses. The internal and external genitals may also be involved.

Terminal haematuria is the most outstanding symptom, followed by symptoms of secondary obstruction and infection.

Numerous ova are carried to the liver, where they penetrate the vessel walls into the parenchymatous tissue. This gives rise to a serious cirrhosis with splenomegaly and accompanying symptoms.

In the lungs the embolic ova produce a necrotizing arteriolitis and parenchymatous tubercles. Attendant right heart hypertrophy is observed.

Ova occasionally reach the central nervous system and give rise to various neurologic disorders.

Diagnosis.

Even in case of clinical suspicion and anamnestic information of exposure, the diagnosis is only based on the detection of ova. In *schistosomiasis haematobium* these are found chiefly in the urine, in *schistosomiasis mansoni* chiefly in the lower digestive tract.

The ova in bilharziasis are not found, as a rule, by handling the urine as for routine microscopy. The examinations of the two cases reported can fully confirm this experience. The WHO Expert Committee on Bilharziasis (7) recommends physical activity before mictation (for instance, riding a stationary bicycle for 10—15 minutes) which is known to accelerate the migration of ova to the urine.

The urine specimen is allowed to sedimentate for 30 to 60 minutes. The bottom layer is centrifuged for 3 minutes at 1000 r. p. m., and the sedi-

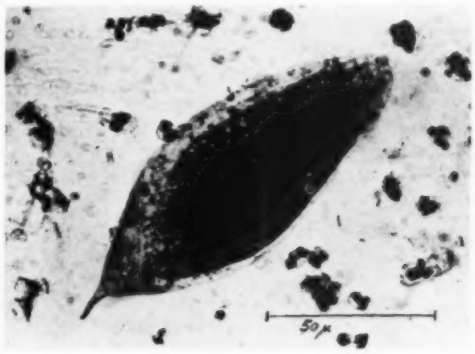

Fig. 2.
An ovum of schistosoma haematobium. Note the terminal spine. Leukocytes and erythrocytes surround.
Preparation of urinary sediment. Dried and stained with methylene blue.

ment is examined by microscope unstained or after staining with methylene blue (Fig. 2). The size of the ova is about 150×60 μ. Characteristic of *schistosoma haematobium* is the terminal delicate spine.

Hatching of the living ova could be seen by the use of a hand lens after diluting the urine with fresh water, the change in osmotic pressure acting as a hatching stimulus in about 5—10 minutes. The next developmental stage — the miracidium — was also observed in detail under the microscope, as it penetrated the shell and liberated itself. This was shown by repeating the dilution process on a slide.

Examining urine specimens for miracidia by the hand lens method after diluting is now recommended as a screen test for bilharziasis in endemic areas (7).

The ova can also be found in biopsy specimens from the urinary bladder wall. This was not performed in the two cases reported.

Treatment.

Emetine hydrochloride is temporarily beneficial, but it does not produce permanent cure (7). In Case 1, a 10 day treatment with emetine stopped the haematuria and brought relief in other symptoms. A control examination of the urine two months later revealed a few ova as expected. At this time "Nilodin" had been procured and a planned oral administration of this drug began. "Nilodin" = "Miracil D" = "lucanthone hydrochloride" is a synthetic, non-metallic thioxanthone compound. Dosage was in both cases 16 mg per kg of body weight daily in a 6 day course and 23 mg per kg in the following 3 day courses. Side-effects in the form of nausea, anorexia, headache and abdominal pain appeared but were not so severe as to warrant interruption of treatment. A foreseen yellow pigmentation of the skin, mainly the plantar surfaces, and of the mucous membranes was seen in both patients. This discolouration disappeared within a few days.

The primary result of the treatment was satisfactory: the haematuria stopped and the urine showed no living ova after the third course. Nothing, however, can be said about any real cure before 6 to 12 months or more have elapsed since the treatment began, and further treatment will probably be necessary. Even in the event of the infection being stopped, the final prognosis must be determined by any irreversible damage to the liver, kidneys or bladder.

Before lucanthone the drugs of choice have been the antimony compounds: potassium antimony tartrate, sodium antimony tartrate, Fuadin and anthiomaline. Messent (4) concludes that "Nilodin" is superior to sodium antimony tartrate and anthiomaline. Watson (5, 6) considers "Nilodin" to be as effective as tartar emetic, more effective than Fuadin and less toxic than either. King (3) reported ova-free urine in 60 per cent 6 months after "Nilodin" treatment. No evaluation of lucanthone hydrochloride can, of course, be deduced from the treatment of the present two cases. The conclusions concerning therapy of the WHO Expert Committee on Bilharziasis is shown in Table 1. (7)

Table 1.

Drug	Treatment technique	Percentage efficiency in S. haematobium infection
Sodium antimony tartrate	Intensive course	85—90
Nilodin	Orally	80—85
Sodium antimony tartrate	Classical course	75—80
Fuadin	Intravenously	60—65
Fuadin	Intramuscularly	50—55
Anthiomaline	Intramuscularly	50—55
Anthiomaline	Intravenously	45—50

Cited from (7)

SUMMARY

The importance of global travelling to the occurrence of cases of endemic diseases in non-endemic areas is stressed by the report of two cases of bilharziasis in Denmark. The methods of diagnosis are described and the characteristic features of schistosoma haematobium infection are briefly outlined. Treatment with "Nilodin" = "Miracil D" = "Lucanthone hydrochloride" is described.

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